New nodules at incidence low-dose CT lung cancer screening

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Non Sibi, Sed Omnibus

등잔 밑이 어둡다
[It is dark under a lamp]

Für Erwin.

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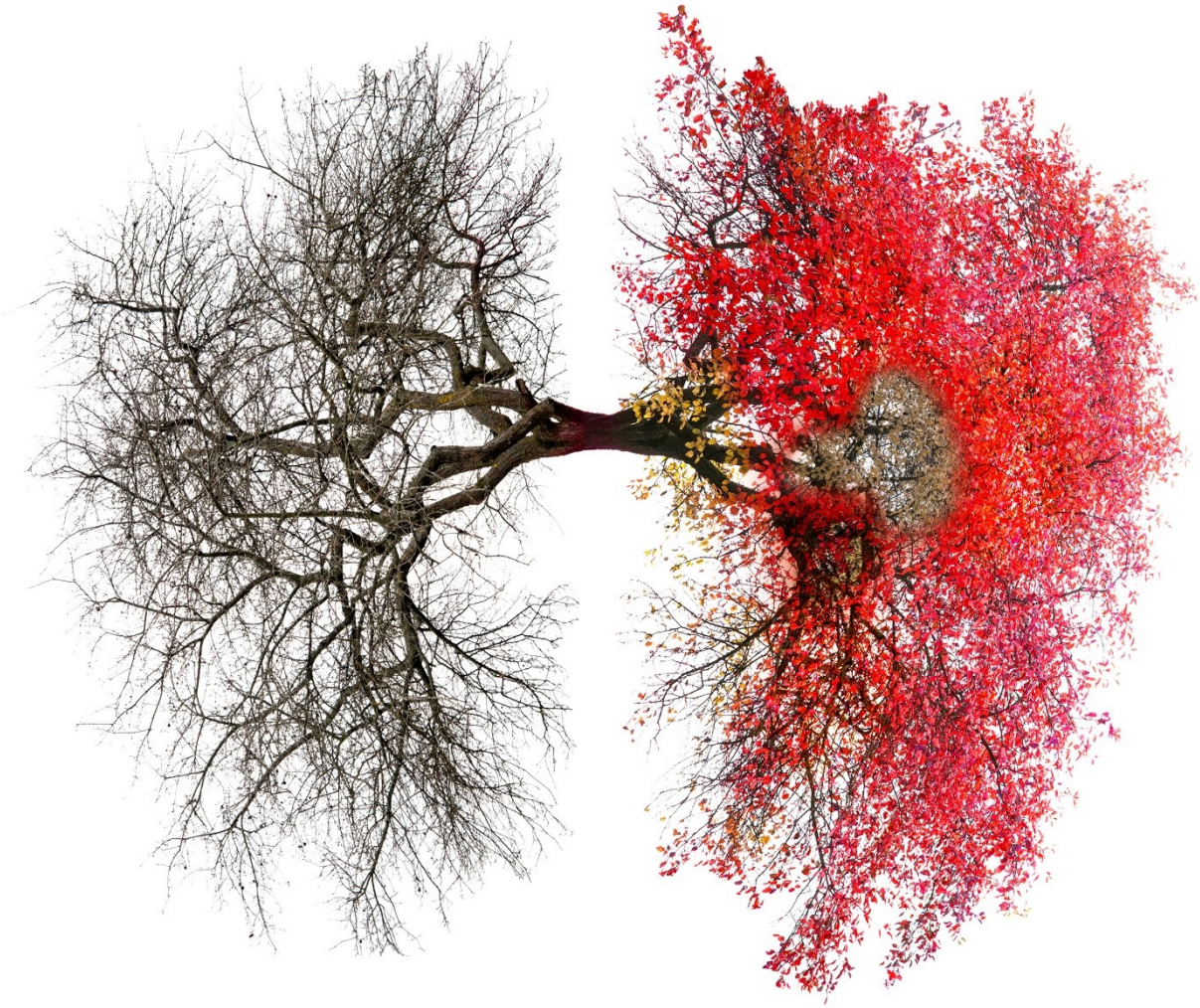
Abbreviations and acronyms

3D	three-dimensional
CI	confidence interval
CT	computed tomography
DANTE	Detection and screening of early lung cancer by Novel imaging Technology and molecular assays
DLSCT	Danish Lung Cancer Screening Trial
ELCAP	Early Lung Cancer Action Project
EUCT	European randomized lung cancer CT screening
GROWCAT	nodule growth category
HU	Hounsfield Units
IQR	inter-quartile range
ITALUNG	Italian Lung cancer Computed Tomography screening trial
LDCT	low-dose computed tomography
LUSI	German Lung Cancer Screening Intervention Study
MDCT	multi-detector computer tomography
MILD	Multi-center Italian Lung Detection Trial
NELSON	Dutch-Belgian Randomized Lung Cancer Screening Trial
NLST	National Lung Screening Trial
NODCAT	nodule size category
NPV	negative predictive value
OR	odds ratio
PLuSS	Pittsburgh Lung Screening Study
PPV	positive predictive value
PVC	percentage volume change
UKLS	United Kingdom Lung Cancer Screening Trial
VDT	volume-doubling time

Part I
Introduction



Chapter 1

General thesis outline

Lung cancer is deadly.

It is estimated that annually 1.6 million deaths are due to lung cancer worldwide, making it the leading cause of cancer-related death.[1–3] The time of diagnosis directly translates to survival, with 5-year survival rates ranging between 12-90% depending on the lung cancer stage.[4] An important factor is that lung cancer often remains symptomless until far progressed and most clinical patients are beyond stage I.[4]

Several studies, including randomized controlled trials, have examined or are examining the possibility of lung cancer screening with low-dose computed tomography (LDCT) to reduce mortality.[5,6] After the American National Lung Screening Trial (NLST) showed a 20% reduced lung cancer mortality when comparing LDCT to conventional chest radiography,[7] most US guidelines now recommend LDCT lung cancer screening for high-risk individuals.[8–10] European stakeholders, however, are awaiting the final results of the Dutch–Belgian lung cancer screening (NELSON) trial.[9,11]

LDCT lung cancer screening consists of a single baseline screening (the first screening round) and multiple annual incidence screening rounds. In lung cancer screening trials, around 22-51% of participants have non-calcified pulmonary nodules at baseline screening.[12–21] However, before the results of this thesis were published, it became apparent that there only was limited evidence concerning new nodules developed after baseline screening, because data were often clustered together with baseline nodules.[8,22]

As will be argued in this thesis, the distinction between baseline nodules and new nodules is crucial and directly affects optimal management. While baseline nodules might have been present for years before detection, new nodules after baseline developed within a short and pre-specified timeframe. Consequently, compared to baseline nodules, new nodules had less time to grow and size cutoffs derived from baseline nodules might be too conservative.

Therefore, the aim of this thesis is to provide evidence for the risk-stratification of new nodules in incidence screening rounds of LDCT lung cancer screening. The development of a new nodule stratification strategy depends on the clarification of several open questions. Next to the knowledge concerning the occurrence and lung cancer probability of new nodules, size cutoffs for initial detection are of key interest.

Similarly, the appropriate risk-stratification strategy of new solid nodules at first follow-up after initial detection should be investigated.

This research is based on the largest European randomized lung cancer screening study – the NELSON trial. The Dutch–Belgian NELSON trial was launched in September 2003 as a multicenter randomized controlled trial to investigate whether LDCT screening would decrease lung cancer mortality by 25% when compared to no screening. Eligible participants were high-risk (ex-)smokers between 50 and 75 years of age. Participants received LDCT screening at baseline, 1 year after baseline, 3 years after baseline, and 5.5 years after baseline. The NELSON trial is the first to employ a volume-based instead of a diameter-based nodule management protocol. Importantly, while any nodule can be characterized by an unlimited number of diameters, it only has one volume.
The results of this research could affect currently ongoing and future lung cancer screening programs as well as clinical practice nodule management guidelines.

The thesis is structured in five sections.
The **first section** contains **Chapters 1-4** and forms the introduction of this thesis. While **Chapter 1** provides the outline of the presented thesis, **Chapter 2** and **Chapter 3** review the evidence from large lung cancer screening trials to create a basis for the assessment of pulmonary nodules detected during lung cancer screening in a more clinical relevant manner, instead of clustering baseline nodules and new nodules together.
The **second section** contains **Chapters 4-7** and focusses on the risk-stratification of new nodules as well as the impact of new nodules on a screening program. **Chapter 4** assesses the occurrence and lung cancer probability of new solid nodules as well as size cutoffs for risk-stratification at initial new nodule detection. **Chapter 5** investigates the optimal new nodule growth-speed and size cutoffs at first follow-up after detection. **Chapter 6** examines whether new nodule characteristics can improve the size-based risk-stratification approach developed in Chapter 4. **Chapter 7** focusses on the appropriate risk-stratification of new subsolid nodules in LDCT lung cancer screening.

The **third section** contains **Chapters 8** and **Chapter 9**. Both Chapters investigate the relationship between the number of (new) nodules detected in a participant at baseline **(Chapter 8)** or incidence screening rounds **(Chapter 9)** and lung cancer probability.
The **fourth section** contains **Chapter 10**, **Chapter 11 and Chapter 12. Chapter 10** discusses the results of this thesis and presents the conclusions, while **Chapter 11** and **Chapter 12** provide the summary.
The **fifth section** contains **Chapters 13-14** and forms the Appendix of this thesis.

Research questions addressed in this thesis

I. What is the occurrence of new nodules in lung cancer screening?
II. What is the lung cancer probability of new nodules in lung cancer screening?
III. What are optimal size cutoffs for new solid nodules at initial detection?
IV. What is the appropriate risk-stratification strategy of new solid nodules at first follow-up after initial detection?
V. What is the proportion of resolving new nodules and how does this affect risk-stratification?
VI. Can new nodule characteristics improve size-based new nodule risk-stratification?
VII. Does the number of nodules detected in a lung cancer screening participant affect their lung cancer probability?

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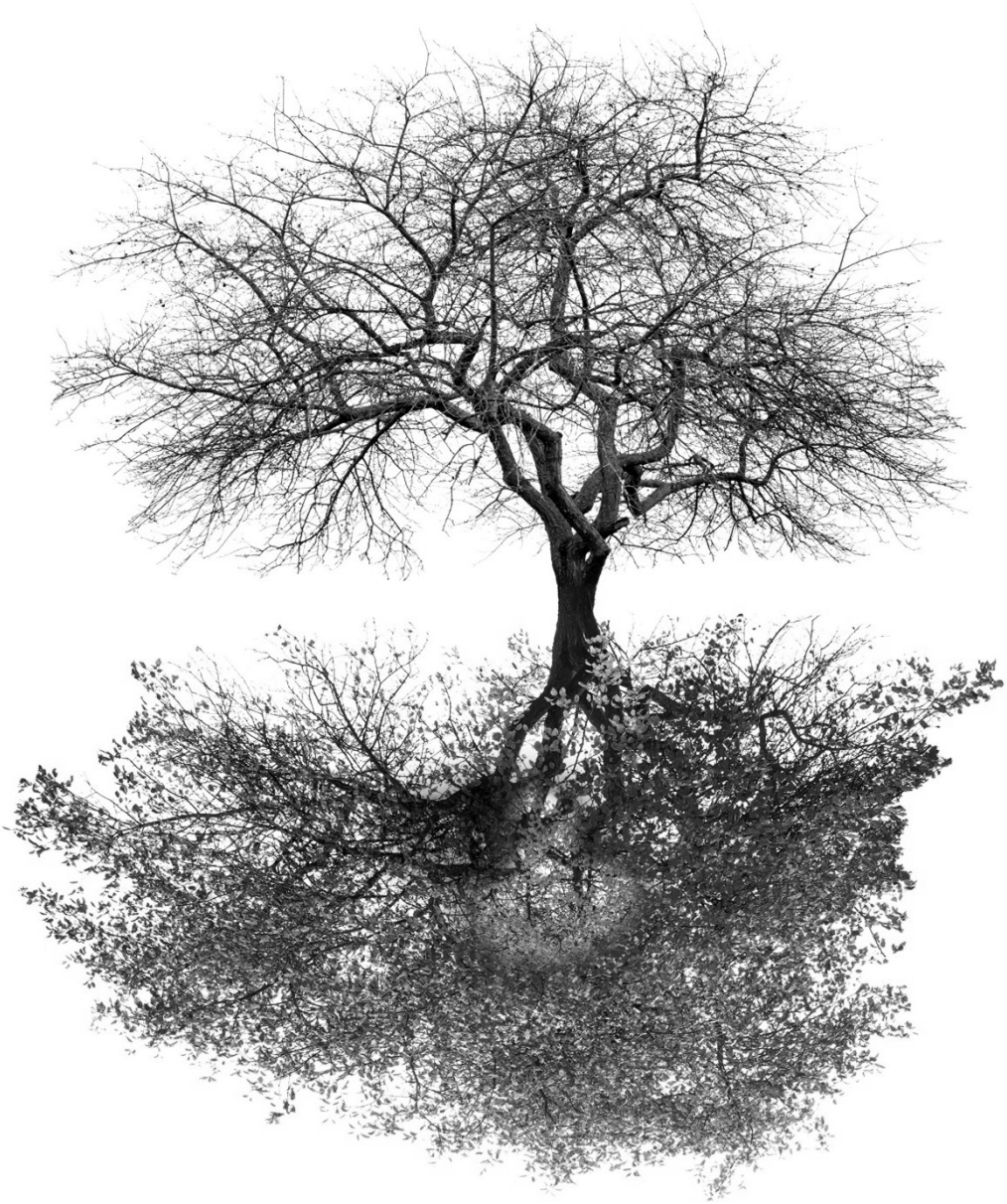
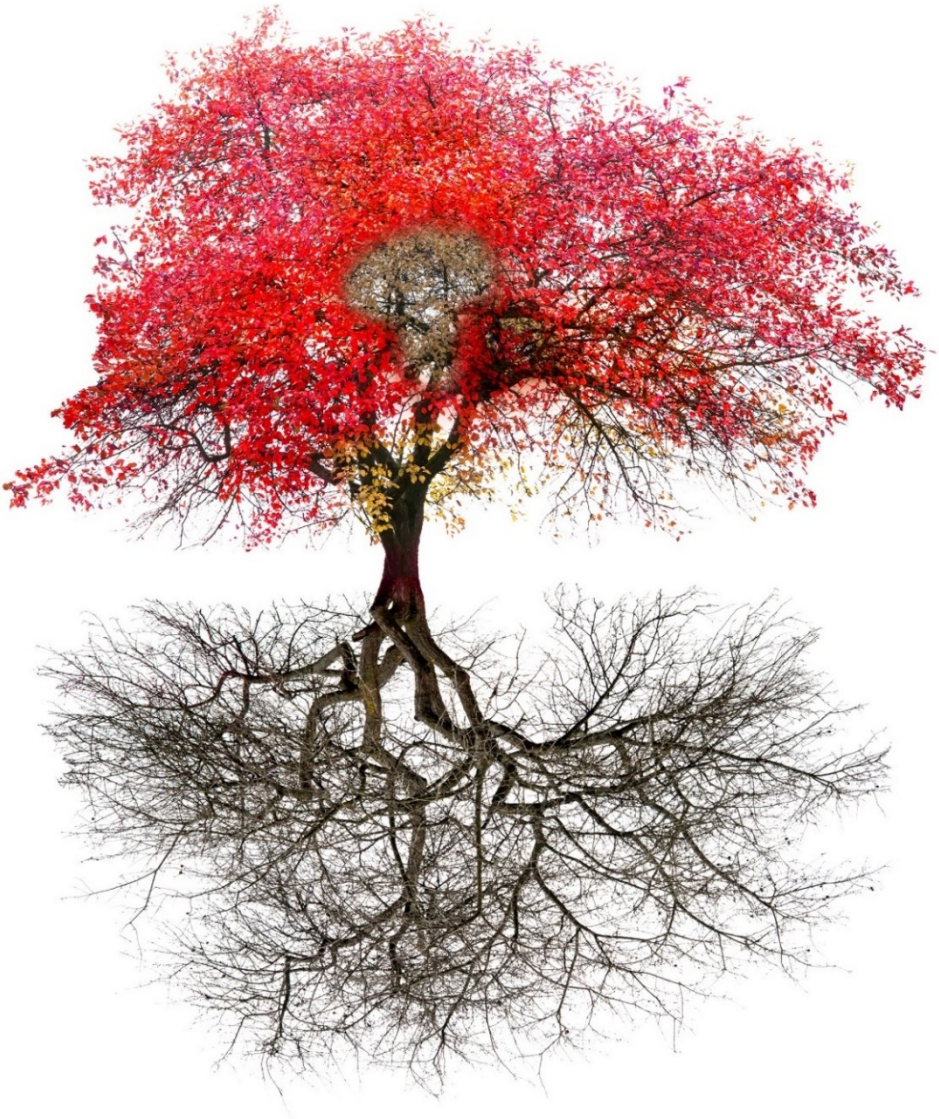


Chapter 2

Small pulmonary nodules in baseline and incidence screening rounds of low-dose CT lung cancer screening

Translational Lung Cancer Research. 2017 Feb; 6(1): 42–51.



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ABSTRACT

Currently, lung cancer screening by low-dose computed tomography (LDCT) is widely recommended for high-risk individuals by US guidelines, but there still is an ongoing debate concerning respective recommendations for European countries. Nevertheless, the available data regarding pulmonary nodules released by lung cancer screening studies could improve future screening guidelines, as well as the clinical practice of incidentally detected pulmonary nodules on routine CT scans. Most lung cancer screening trials present results for baseline and incidence screening rounds separately, clustering pulmonary nodules initially found at baseline screening and newly detected pulmonary nodules after baseline screening together. This approach does not appreciate possible differences among pulmonary nodules detected at baseline and firstly detected at incidence screening rounds and is heavily influenced by methodological differences of the respective screening trials. This review intends to create a basis for assessing non-calcified pulmonary nodules detected during LDCT lung cancer screening in a more clinically relevant manner. The aim is to present data of non-calcified pulmonary baseline nodules and new non-calcified pulmonary incident nodules without clustering them together, thereby also simplifying translation to the clinical practice of incidentally detected pulmonary nodules. Small pulmonary nodules newly detected at incidence screening rounds of LDCT lung cancer screening may possess a greater lung cancer probability than pulmonary baseline nodules at a smaller size, which is essential for the development of new guidelines.

Introduction

Lung cancer remains a leading cause of cancer-related death worldwide.[1] Various efforts have been made to contain the extent of the disease and an early detection of lung cancer is crucial for successful treatment and prolonged survival.[2,3] Lung cancer screening studies using low-dose computed tomography (LDCT) were set up all over the world, to assess the feasibility of detecting lung cancer in high-risk individuals as early as possible.[4–6] The National Lung Screening Trial, which is the largest randomized-controlled LDCT lung cancer screening trial, reported a relative reduction in lung cancer-specific mortality of 15-20% when comparing chest X-ray and LDCT screening.[7] Currently, lung cancer screening by LDCT is widely recommended for high-risk individuals by US guidelines.[8–15] However, there still is an ongoing debate if screening should be recommended for high-risk individuals in Europe, and further evidence is needed.[16] Nevertheless, the vast data on (small) pulmonary nodules provided by the lung cancer screening trials enable further insights in the clinical management of pulmonary nodules and the development of future screening guidelines.

Most LDCT lung cancer screening trials present results for baseline and incidence screening rounds separately and elaborate reviews of this data were published before.[4,5,17,18] Although comparing screening rounds provides valuable information about a trial's lung cancer screening performance in general, this approach does not appreciate the possible differences among nodules firstly detected during baseline and incidence screening rounds and is heavily influenced by the differences in methodology of the respective LDCT lung cancer screening trials. For instance, a lung cancer screening trial with an aggressive baseline screening follow-up strategy may report lower cancer rates during incidence screening rounds, than a trial with a less aggressive strategy at baseline screening, even though the overall lung cancer rate is similar. However, only limited evidence concerning the different groups of pulmonary nodules identified is provided. Non-calcified pulmonary nodules detected at baseline screening consist of a combination of nodules that may have been present for years and a fewer number of more recently developed nodules. Non-calcified pulmonary nodules firstly detected during incidence screening may be entirely new (not present on a previous screen), not new (missed on a previous screen), or below the detection

threshold of the respective LDCT lung cancer screening trial on the previous screen (hence, these are growing nodules). Unfortunately, lung cancer screening trials present their data concerning lung cancer rates in the various groups of non-calcified pulmonary nodules differently and the definitions of incidence nodules vary widely.[4,5,10,16] The recently released British Thoracic Society Guidelines for the Investigation and Management of Pulmonary Nodules addresses this issue by stating that there is little evidence for the management of new incident nodules that appear on follow-up CTs.[19]

This review intends to create a basis for assessing non-calcified pulmonary nodules detected during lung cancer screening in a more clinically relevant manner. The aim is to present detection rates of non-calcified pulmonary baseline nodules and non-calcified pulmonary incident nodules not present on a previous scan (thus new) without clustering them together. Furthermore, lung cancer probabilities of non-calcified baseline and new non-calcified incident pulmonary nodules will be assessed, as well as the lung cancer risk for participants with such nodules. As the majority of trials do not explicitly state rates concerning new non-calcified pulmonary incident nodules, only limited evidence is available for this nodule group. This review focusses mainly on the following European lung cancer screening trials: United Kingdom lung screening (UKLS) trial, Italian detection and screening of early lung cancer by novel imaging technology and molecular assays (DANTE) trial, Danish lung cancer screening trial (DLCST), Dutch–Belgian lung cancer screening trial (NELSON), Italian lung study (ITALUNG), German lung cancer screening intervention study (LUSI); American lung cancer screening trials: National lung screening study (NLST), early lung cancer action project (ELCAP), Mayo CT Screening study (Mayo trial), Pittsburg Lung Screening Study (PLuSS); and the international early lung cancer action project (IELCAP) trial.

Pulmonary nodules in baseline screening rounds of LDCT lung cancer screening

Prevalence of non-calcified pulmonary nodules at baseline rounds of LDCT lung cancer screening

The prevalence of pulmonary nodules at baseline rounds of LDCT lung cancer screening depends on the methodology of the respective screening approach, such as the CT protocol or the use of an artificial detection limit. Additionally, a higher prevalence of certain diseases, such as histoplasmosis, may influence the number of detected solitary lung nodules.[20] Most European and American trials with no detection limit (PLuSS and Mayo trial) or detection limit of 3mm or 15mm^3 (NELSON and UKLS) reported a non-calcified pulmonary nodule prevalence in between 41-51% of baseline participants (Table 1 and Table 2).[21–24] However, the ELCAP and DLCST trial, which both did not employ a detection limited, reported lower non-calcified pulmonary nodule rates in participants at baseline (23% [233/1,000] and 22% [447/2,052] respectively).[25,26] These differences could be explained by a plethora of factors, such as differences in methodology, patient population, infectious disease prevalence, etc.. For instance, the difference between the Mayo trial (51% [780/1,520] non-calcified pulmonary nodule baseline prevalence) and ELCAP trial (23% [233/1,000] non-calcified pulmonary nodule baseline prevalence) has been attributed to differences in slice thickness during CT detection.[5,25,27] Furthermore, the ELCAP trial only reported nodules of participants with less than six nodules, possibly reducing the non-calcified pulmonary nodule baseline rate.[25]

	UKLS [24]	DANTE [4,34]	DLCST [4,26]	NELSON [4,23,33]	ITALUNG [4,29]	LUSI [4,30]
Participants						
Received CT screening	1994	1276	2052	7557	1406	2029
Age, mean (SD)	67 (4)	65 (5)	57 (5)	59 (6)	61 (4)	58 (5)
Pack Years, mean (SD)	NA	47 (25)	36 (13)	42 (19)	43 (18)	36 (18)
Nodule detection limit	≥15mm^3 or ≥3mm	None reported	None reported	≥15mm^3	≥5mm	≥5mm
Participants with lung cancer	42/1994 (2.1%)	28/1276 (2.2%)	17/2052 (0.8%)	70/7557 (0.9%)	20/1406 (1.4%)	22/2029 (1.1%)
Participants with NCNs	1015/1994 (50.9%)	NA	447/2052 (21.8%)	3816/7557 (50.5%)	426/1406 (30.3%)	540/2029 (26.6%)
% with lung cancer	42/1015 (4.1%)	NA	17/447 (3.8%)	70/3816 (1.8%)	20/426 (4.7%)	22/540 (4.1%)
% of NCNs being lung cancer	NA	NA	17/560 (3.0%)	74/8623 (0.9%)	21/639 (3.3%)	NA
Lung cancer						
Stage I	28/42 (66.7%)	16/28 (57.1%)	9/17 (53.0%)	48/74 (64.9%)	10/21 (47.6%)	18/22 (81.8%)
Histology						
Adenocarcinoma†	25/42 (59.5%)	17/28 (60.7%)	12/17 (70.6%)	37/74 (50.0%)	10/21 (47.6%)	15/22 (68.2%)
Squamous-cell carcinoma	12/42 (28.6%)	8/28 (28.6%)	2/17 (11.8%)	15/74 (20.3%)	6/20 (30.0%)	3/22 (13.6%)
Small-cell Lung cancer	3/42 (7.1%)	2/28 (7.1%)	0	1/74 (1.4%)	1/21 (4.7%)	1/22 (4.5%)
Others	2/42 (4.8%)	1/28 (3.6%)	3/17 (17.6%)	21/74 (28.4%)	4/21 (19.0%)	3/22 (13.6%)

Table 1: Baseline results of selected European low-dose computed tomography lung cancer screening trials.
UKLS=United Kingdom lung screening trial, DANTE=detection and screening of early lung cancer by novel imaging technology and molecular assays, DLCST=Danish lung cancer screening trial, NELSON=Dutch–Belgian lung cancer screening trial, ITALUNG=Italian lung study, LUSI=German lung cancer screening intervention study, SD=standard deviation, NCNs=non-calcified pulmonary nodules, NA=not available.
† Bronchioloalveolar carcinomas are considered adenocarcinomas.

	NLST [28,35]	ELCAP[25]	IELCAP [6]	Mayo† [22]	PLuSS† [5,21]
Participants					
Received CT screening	26309	1000	31567	1520	3642
Age, mean (SD)‡ or median (IQR)§	NA	67 (NA)§	62 (NA)§	59 (NA)‡	59 (NA)‡
Pack Years, mean (SD)‡ or median (IQR)§	NA	45 (NA)§	30 (NA)§	45 (NA)§	47 (33-62)§
Nodule detection limit	≥4mm	None reported¶	≥5mm	None reported	None reported
Participants with lung cancer	270/26309 (1.0%)††	27/1000 (2.7%)	405/31567 (1.3%)	31/1520 (2.0%)	53/3642(1.5%)
Participants with NCNs	7041/26309 (26.8%)	233/1000 (23.3%)	4186/31567 (13.3%)	780/1520 (51.3%)	1477/3642 (40.6%)
% with lung cancer	267/7041 (3.8%)	27/233 (11.6%)	405/4186 (9.7%)	31/780 (4.0%)	53/1477 (3.6%)
% of NCNs being lung cancer	NA	27/363 (7.4%)	NA	31/1646 (1.9%)	53/2497 (2.1%)
Lung cancer					
Stage I	155/270 (57.4%)	23/27 (85.2%)	348/405 (85.9%)	22/31 (71.0%)	31/53 (58.5%)
Histology					
Adenocarcinoma‡‡	156/270 (57.8%)	21/27 (77.8%)	NA	23/31 (74.2%)	NA
Squamous-cell carcinoma	47/270 (17.4%)	1/27 (3.7%)	NA	4/31 (12.9%)	NA
Small-cell Lung cancer	15/270 (5.6%)	0	NA	2/31 (6.5%)	1/53 (1.9%)
Others	52/270 (19.3%)	5/27 (18.5%)	NA	2/31 (6.5%)	NA

Table 2: Baseline results of selected American low-dose computed tomography lung cancer screening trials and the IELCAP trial.

NLST=National lung screening study, ELCAP=early lung cancer action project, IELCAP=international early lung cancer action project, Mayo=Mayo CT Screening study, PLuSS=Pittsburg
Lung Screening Study, SD=standard deviation, IQR=interquartile range, NCNs=non-calcified pulmonary nodules, NA=not available.
† *The Mayo and PLuSS trials reported their baseline findings including lung cancers found in baseline nodules during incidence screening rounds.*
¶ *Participants with more than 6 NCNs were not reported as having lung nodules.*
†† *Low-dose CT detected lung cancer cases.*
‡‡ Bronchioloalveolar carcinomas are considered adenocarcinomas.

Strengthening the case for a higher non-calcified pulmonary nodule rate at baseline, at least in the European smoker or former smoker population, are the recently released results of the UKLS trial's baseline round. This trial shared an analogous methodology with the NELSON trial and confirmed a non-calcified pulmonary nodule baseline prevalence in 51% of the participants for the respective screening setting.[23,24] Trials with a detection limit of 4mm or greater (IELCAP, NLST, ITALUNG, LUSI) reported a lower non-calcified pulmonary nodule rate of between 13-30% at baseline.[6,28–30] This suggests that a great number of non-calcified pulmonary nodules at baseline are small pulmonary nodules. Of the trials with no or a low detection limit, the Mayo trial reported that 39% (307/780) of participants only had non-calcified pulmonary nodules smaller than 4mm and the NELSON trial found that 56% (4,861/8,623) of the non-calcified pulmonary nodules detected at baseline were smaller than 50mm^3 (roughly 4.7mm).[22,23,27] Within the baseline round of the DLCST trial, 66% (371/560) of the non-calcified pulmonary nodules were below 5mm and in baseline participants of the ELCAP trial, the largest non-calcified pulmonary nodule was smaller than 5mm in 58% (136/233).[25,26,31]

Concluding, evidence from trials with no or a low detection limit indicates that 22-51% of heavy smokers and former heavy smokers have non-calcified pulmonary nodules at baseline screening. Of the non-calcified pulmonary nodules detected at baseline, possibly up to 56% are small pulmonary nodules below 50mm^3 or 5mm.

Lung cancer risk of participants with non-calcified pulmonary nodules at baseline and lung cancer probability of non-calcified pulmonary baseline nodules

Unfortunately, data regarding the overall lung cancer risk of participants with baseline nodules is not frequently described. Trials rather report how many participants are diagnosed with lung cancer per round, irrespective in which round the nodule was found initially. However, information about the overall lung cancer risk is crucial, since it could directly influence the clinical practice approach of incidentally found lung nodules in smokers and provide essential information for the development of new guidelines.

The Mayo trial (5-year results) and PluSS trial (3-year result) report that 4% ([31/780] and [53/1,477] respectively) of participants with a non-calcified pulmonary nodule at baseline developed cancer in such a nodule within their screening program.[21,22] Both

trials did not employ a detection limit. The NELSON trial, which used a 15mm^3 (roughly 3mm) detection limit, reported a 2-year lung cancer risk of 3% (94/3,189) for Dutch participants with baseline nodules.[32]

Regarding the probability of a non-calcified pulmonary baseline nodule being diagnosed as lung cancer eventually, the Mayo trial (5-year results) and PLuSS trial (3-year results) reported that 2% ([31/1,646] and [53/2,497] respectively) of the non-calcified baseline nodules turned out to be lung cancer.[21,22]

The other trials included here, only reported the baseline detection rate, thus the number of lung cancers found in participants at baseline, ranging between 1-3% for all participants,[6,23–25,29–31,33,34] and 2-11% for participants with non-calcified pulmonary baseline nodules.[6,23–25,29–31,33,35] During baseline screening, the probability of a non-calcified pulmonary baseline nodule being detected as lung cancer ranged between 1-7.4%.[23,26,29,32] In particular, the ELCAP and IELCAP trial reported very high lung cancer rates (12% [27/233] and 10% [405/4,186] respectively) for participants with non-calcified pulmonary nodules during baseline screening.[6,25] However, as demonstrated previously, these trials also reported a very low non-calcified pulmonary nodule overall detection rate.[6,25] Apparently, the screening methodology of these studies enabled an efficient manner of recognizing individuals with high-risk pulmonary nodules, while potentially not detecting or registering unsuspicious nodules.

As mentioned before, the UKLS and NELSON trial shared a similar screening methodology; however, the participant recruiting strategy differed significantly. While inclusion in the NELSON trial was mainly based on age and smoked pack-years,[23,36] the UKLS trial used a multivariate conditional logistic regression model (including: smoking duration, selected prior respiratory diseases, occupational exposure to asbestos, prior diagnosis of malignant tumors and early onset family history of lung cancer) based on the Liverpool Lung Project.[24,37,38] The UKLS trial included participants only if their calculated 5-year lung cancer risk was more or equal to 5%.[24] This difference in selection methodology resulted in an older screening population in the UKLS if compared to the NELSON trial (mean age: 67 vs. 59 years) and an increased lung cancer baseline detection rate in participants with non-calcified pulmonary baseline nodules (4.1% [42/1,015] vs. 1.8% [70/3,816]).[23,24,33] This unique comparison, which is made possible due to the similar screening methodology, demonstrates the impact of pre-test probability and the limited comparability even of methodologically similar lung cancer screening trials.

Concluding, the sparse existing evidence from the Mayo, PLuSS and NELSON trial indicates that 3-4% of heavy smokers or former heavy smokers with non-calcified pulmonary nodules at baseline screening will be diagnosed with lung cancer in such a nodule within 2-5 years (assuming similar epidemiology as in these trials). However, as demonstrated by baseline lung cancer detection rates of the other mentioned trials, depending on screening protocol and disease prevalence within the screened population, the number may be significantly higher. The translation from lung cancer screening trials to clinical practice of incidentally detected nodules relies on careful assessment of the study population from which the data was generated.

Stage and histology of lung cancers found in non-calcified pulmonary baseline nodules

Only the Mayo and PLuSS trial reported data in a way that enabled assessment of lung cancers found in non-calcified pulmonary baseline nodules across all screening rounds. Most lung cancers detected in a non-calcified pulmonary baseline nodule were stage I (Mayo: 71% [22/31]), PLuSS: 59% [31/53]).[21,22] Only the Mayo trial provided information concerning the histology of lung cancer found in non-calcified pulmonary baseline nodules during all screening rounds. The majority (74% [23/31]) of lung cancers were adenocarcinomas, followed by squamous-cell carcinomas (13% [4/31]) and small-cell lung cancer (7% [2/31]).

The results concerning stage and histology at baseline screening are equivocal. The ELCAP trial, IELCAP trial, and LUISI trial reported a very high proportion of stage I lung cancer at baseline (82%-86%).[6,25,30] The other trials, including the two largest, randomized controlled trials (NLST and NELSON), reported lower numbers regarding stage I lung cancers (48-67%).[7,23,24,29,30,34] There is no data available about differences in stage or histology distribution between non-calcified pulmonary baseline nodules identified as lung cancers at baseline compared to non-calcified pulmonary baseline nodules identified as lung cancers in later rounds. Differences between lung cancers found at baseline and incidence rounds, as published for instance by the ELCAP trial,[39] cannot be used for the here performed assessment, since observed variances may be due to lung cancers found in newly detected nodules.

Concluding, lung cancers detected in non-calcified pulmonary baseline nodules are mostly adenocarcinomas. Current evidence suggests that only a small fraction is small-cell lung cancer. At baseline, lung cancers are stage I in 48-86% of the cases.

Data concerning stage distribution of lung cancers detected in baseline nodules at subsequent rounds is sparse.

New non-calcified pulmonary nodules in incidence screening rounds of LDCT lung cancer screening

Prevalence of new non-calcified pulmonary nodules in incidence rounds of LDCT lung cancer screening

As pointed out by several studies and the recently released British Thoracic Society guidelines for the Investigation and Management of Pulmonary Nodules, little evidence exists concerning pulmonary incident nodules that appear after baseline screening and are not visible in retrospect.[10,19,40] In 2005, the Fleischner society reported, citing the Mayo trial, that 10% of screening participants develop a new nodule not present in retrospect within a 1-year interval, and the PLuSS trial described that 7% [256/3,423] of their participants developed a new nodule in the same interval.[21,27,41] Numbers from the ELCAP and IELCAP publications suggest annual new nodule rates of 3% (40/1,184) and 5% (1,460/27,456) respectively in LDCT lung cancer screening.[6,42] In the annual screening round of the NELSON trial, 5% (344/7,295) of the participants developed a new non-calcified solid nodule, while a total of 11% (787/7,295) of participants developed a new non-calcified solid nodule within the first two incidence screening rounds (3 years after baseline).[40]

The NELSON trial reported that 57% (697/1,222) of the newly detected nodules were small pulmonary nodules with a volume less than 50mm^3 (roughly 4.7mm).[40] The ELCAP trial reported that in the 30 participants with high-resolution CT confirmed new non-calcified pulmonary incident nodules, the largest nodule had had a diameter less than 5mm in 53% (16/30) of participants,[42] and in 37% (70/191) of participants with new non-calcified pulmonary incident nodules in the Mayo trial, the nodules were smaller than 4mm.[27]

Concluding, current evidence suggests that 3-10% of LDCT lung cancer screening participants may develop a new non-calcified pulmonary incident nodule annually and up to 57% of these nodules are pulmonary nodules smaller than 50mm^3 or 5mm.

Lung cancer risk of participants with new non-calcified pulmonary incident nodules and lung cancer probability of new non-calcified pulmonary incident nodules

The evidence regarding lung cancer probability of new non-calcified pulmonary incident nodules is scarce. Furthermore, differing methodologies of trials make the numbers hardly comparable.

The NELSON trial recently reported that 6% (49/787) of participants with a new non-calcified solid nodule developed lung cancer in such a nodule, with 4% (50/1,222) of the new non-calcified solid incident nodules proving to be lung cancer.[40] The ELCAP trial reported that 10% (4/40) of participants with new non-calcified pulmonary incident nodules on LDCT had lung cancer in a new nodule, and the IELCAP reported this was the case for 5% (74/1,460) of its participants.[6,21,42] The Mayo trial found a lower rate of 1.6% (3/191).[27] However, the Mayo trial reported a substantially higher new nodule rate than the other trials (see above) and the clinic where the trial was performed is located in an area with a high prevalence of histoplasmosis.[20] This may explain why the Mayo trial found the highest new nodule rate, but the lowest cancer rate in new non-calcified pulmonary incident nodules. Without providing numbers, the NLST reported that detection of new non-calcified pulmonary incident nodules in the second incidence screening round was predictive for cancer if compared to stable nodules.[43]

Concluding, there is only little evidence concerning the lung cancer risk of participants with new non-calcified pulmonary incident nodules. The two large studies that provide data (IELCAP and NELSON trial) show that in 5-6% of participants with new non-calcified pulmonary incident nodules, such a nodule proves to be lung cancer. The only available numbers concerning lung cancer probability of new (solid) incident nodules come from the NELSON trial, where 4% of the new solid non-calcified pulmonary incident nodules proved to be lung cancer.

Stage and histology of lung cancers found in new non-calcified pulmonary incident nodules

The only trial to provide explicit data concerning lung cancer stage, as well as histology for new incident nodule lung cancer, is the NELSON trial. It was found that 68% (34/50) of the new incident nodule lung cancers were detected at stage I.[40] Of the detected lung cancers 38% (19/50) were adenocarcinomas, 22% (11/50) were squamous-cell carcinoma, and 10% (5/50) were small-cell lung cancer. The IELCAP trial reported

that 86% (64/74) of lung cancers in patients with new non-calcified pulmonary incident nodules was detected at stage I.[6]

Concluding, it appears that thorough LDCT lung cancer screening can detect most new nodule lung cancer at an early and still treatable stage. There is insufficient data to make definite statements about cancer histology of new nodule lung cancer detected in incidence screening rounds of LDCT lung cancer screening.

Comparing lung cancer probability of small pulmonary nodules detected at baseline and newly detected during LDCT incidence screening

Due to the differences in screening methodology, baseline nodules and new incident nodules should not be compared across lung cancer screening trials. Valid conclusions can only be reached through analysis within one screening trial. Furthermore, because only a subgroup of participants develops new incident nodules, trials have to be large enough to provide a significant sample size of new nodule lung cancers.

The IELCAP trial reported a cancer rate of 10% (405/4,186) in participants with baseline nodules and a cancer rate of 5% (74/1,460) for participants with new non-calcified pulmonary incident nodules.[6] However, it is crucial to note that the screening method for baseline and incidence screening deviated significantly. While during the baseline screening round only nodules greater or equal to 5mm were registered, there was no detection limit for new non-calcified pulmonary incident nodules at incidence screening rounds.[6] The cancer rate at baseline excluded participants who only had nodules smaller than 5mm, which as seen in other trials comprise the largest group of nodules, but the cancer rate for new incident nodules included them, rendering the numbers incomparable.

The ongoing NELSON trial did not yet provide the cancer rate of nodules detected at baseline for the overall screening. A comparison of cancer probability of new non-calcified pulmonary incident nodules and non-calcified pulmonary baseline nodules has to be made indirectly. In the baseline screening round of the NELSON trial, 1% (70/7,557) of participants were detected with lung cancer,[23] and within the first three screening rounds, 3% (200/7,582) participants had screen-detected lung cancer

(including 44 cancers detected in new solid non-calcified pulmonary incident nodules).[33,40] As mentioned before, the 2-year cancer risk of participants detected with baseline nodules in the NELSON trial has been reported to be 3% (94/3,189). The cancer risk of participants detected with new solid non-calcified pulmonary incident nodules was 6% (49/749). Comparing these numbers, new solid non-calcified pulmonary incident nodules appear to have a higher lung cancer probability than do non-calcified baseline nodules. This is underlined by the fact, that the overall cancer risk of participants with a new solid non-calcified pulmonary incident nodule was similar to the risk of participants with a suspicious nodule at baseline that required received further follow-up.[40]

New incident nodules are considered fast-growing and some lung cancer screening trials and screening guidelines anticipated this by using different cut-off values for baseline nodules and new incident nodules.[6,44,45] The NELSON trial showed that there is a significant difference in the lung cancer probability of small pulmonary non-calcified nodules already present at baseline and new non-calcified pulmonary incident nodules. Within the NELSON trial, baseline nodules that were smaller than 100mm^3 (roughly 5.8mm) had a lung cancer probability of about 0.5-0.7%, which statistically did not differ from participants without baseline nodules.[32] It was concluded that these nodules do not necessitate follow-up. However, this does not apply in case of new solid non-calcified pulmonary incident nodules, where 3% of participants whose largest new nodule was smaller than 100mm^3 (roughly 5.8mm) were eventually diagnosed with lung cancer, with 2% (15/819) of new solid non-calcified incident nodules smaller than 100mm^3 (roughly 5.8mm) found to be lung cancer.[40] These findings caused the NELSON investigators to propose different cut-off values for the follow-up of baseline nodules and new solid non-calcified pulmonary incident nodules. Based on the results of the NELSON trial, non-calcified baseline nodules smaller than 100mm^3 (0.6% lung cancer probability) or 5mm (0.4% lung cancer probability) may continue in regular screening, non-calcified baseline nodules 100-300mm^3 (2.4% lung cancer probability) or 5-10mm (1.3% lung cancer probability) represent an indeterminate subgroup requiring follow-up with volume doubling time measurement (<600 days necessitates further follow-up), and, non-calcified baseline nodules greater than 300mm^3 (16.9% lung cancer probability) or 10mm (15.2% lung cancer probability) should be referred for immediate diagnostic evaluation.[32] New non-calcified pulmonary incident nodules require a more aggressive follow-up strategy and only a new non-

calcified solid incident nodule smaller than 27mm^3 (0.5% lung cancer probability) or 3.7mm (0.6% lung cancer probability) should continue regular screening, new non-calcified solid incident nodules between 27-<206mm^3 (3.1% lung cancer probability) or 3.7-<8.2mm (3.0% lung cancer probability) represent an indeterminate subgroup requiring follow-up and volume doubling time measurement, and new non-calcified pulmonary incident nodules greater or equal 206mm^3 (16.9% lung cancer probability) or 8.2mm (14.2% lung cancer probability) should be referred for immediate diagnostic evaluation.[40] This verifies part of the LungRads guidelines as provided by the American College of Radiologists.[44] It has been suggested that the findings regarding new nodules may be translated directly into routine clinical practice for the respective risk group (i.e. smokers or former heavy smokers) outside a screening program, if the nodule can be proven to be newly developed within 1-2 years.[40,46]

The explanation for the different lung cancer probabilities at smaller sizes of non-calcified baseline and new non-calcified pulmonary incident nodules could be the fact that compared to new incident nodules, baseline nodules had more time to grow before their first detection. Therefore, growing baseline nodules which possess a higher lung cancer probability are larger, while even fast-growing new nodules may still be relatively small at initial detection. Furthermore, new non-calcified pulmonary incident nodules may be inherently more likely to be cancer than non-calcified baseline nodules. Nevertheless, more evidence is necessary to expand existing conclusions.

Conclusion

Reporting lung cancer screening results per round, without providing overall cancer risks of participants detected with non-calcified pulmonary nodules at baseline or with new non-calcified pulmonary incident nodules at subsequent screening rounds, only provides limited information on lung cancer probabilities of the respective nodule groups. Much evidence is to gain from a more standardized manner of reporting, including subgrouping of the detected nodules according to the moment of the first detection, such as baseline nodule or new incident nodule. This would also simplify the translation to the current clinical practice of incidentally detected nodules.

Around half of heavy smokers or former heavy smokers may present with non-calcified pulmonary nodules at baseline screening. Though there only is limited evidence, it can be expected that at least 3-4% of these individuals will be diagnosed with lung cancer

in a non-calcified pulmonary baseline nodule within the next 2-5 years. A majority of non-calcified pulmonary nodules detected at baseline are small pulmonary nodules smaller than 50mm^3 or 5mm and possess a low lung cancer probability.

Furthermore, 3-10% of heavy smokers or former heavy smokers develop a new non-calcified pulmonary incident nodule annually, and these nodules prove to be lung cancer in 5-6% of participants. Internal comparison of the NELSON trial provided evidence that new non-calcified pulmonary incident nodules possess a greater lung cancer probability than baseline nodules at a smaller size. This may be due to the reduced time they had to grow before first nodule detection, or due to an inherently increased cancer probability. Therefore, small pulmonary non-calcified nodules detected newly at lung cancer incidence screening rounds should be followed up more aggressively than small pulmonary non-calcified pulmonary nodules detected at baseline screening. Additionally, for the respective risk population, the findings may be extrapolated for the management of incidentally detected nodules in routine clinical care, outside a screening program.

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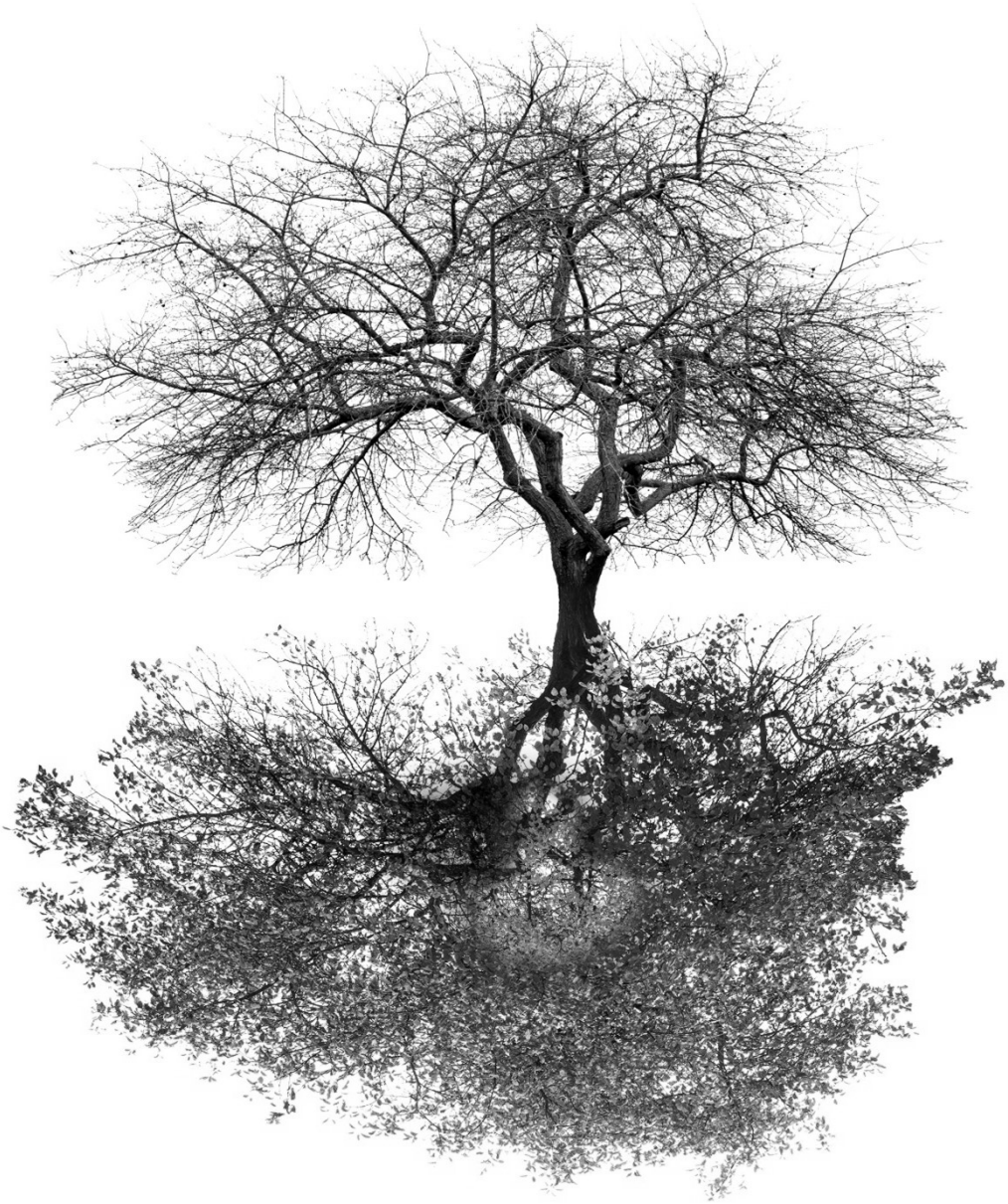

Chapter 3

Management of baseline and new sub-solid nodules in CT lung cancer screening

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Introduction

While reading thoracic CT examinations, three different sub-types of pulmonary nodules are differentiated based on the nodule's density. Until now, most existing evidence concentrated on solid lung nodules. However, in recent years gradually more studies are published focusing on subsolid nodules including pure ground-glass (nonsolid) nodules (GGNs) and part-solid nodules. A GGN is defined as a circumscribed area of increased pulmonary attenuation with preservation of the bronchial and vascular margins. When part of the ground-glass opacity completely obscures the parenchyma, the nodule is defined as part solid.

In baseline rounds of CT lung cancer screening, part-solid nodules comprise a higher risk of malignancy than do solid nodules.[1] Management of subsolid nodules in lung cancer screening trials and incidentally detected subsolid nodules in clinical practice is based on nodule size and growth.[2] In most guidelines, no differentiation is made between subsolid nodules already present at a previous CT examination and new subsolid nodules. Recently, it was shown that new solid nodules detected in CT lung cancer screening have a significantly higher lung cancer probability at smaller nodule size compared to baseline solid nodules and need lower size cut-offs.[3] Some guidelines, such as the British Thoracic Society (BTS) guideline and Lung-RADS, have incorporated the higher malignancy risk in solid new nodules.[4,5] However, the question remains whether new subsolid nodules should be followed more aggressively as well.

Subsolid nodules detected at baseline and incident lung cancer screening

Several lung cancer screening trials have reported the prevalence of subsolid nodules. In a large prospective cohort, the International Early Lung Cancer Action Program (I-ELCAP), it was found that at least one nonsolid nodule was detected in 4.2% of participants at baseline, and 5.0% had at least one part-solid nodule at baseline.[6] As far as we know, only I-ELCAP published separate reports on the prevalence of new GGNs and part-solid nodules.

A new GGN was detected in 0.7% (485/64,677) annual repeat screenings. Eleven new GGNs nodules were diagnosed as adeno-carcinoma, all stage IA. In both baseline and new GGNs, lung cancer was diagnosed only in growing GGNs, and always was

stage I, regardless of nodule size. Seventy-eight months (median) after lung cancer diagnosis, none of the patients had died from lung cancer. It was concluded that screen-detected GGNs either present at baseline or new at incidence screening can be followed safely with annual low-dose computed tomography (LDCT).[6]

In 0.8% (541/64,667) annual repeat screenings a new part-solid nodule was identified in the I-ELCAP.[7] Of these new part-solid nodules, 69.7% resolved or decreased in size at follow-up. Twenty-eight (5.2%) of the 541 new part-solid nodules were proven to be lung cancer, all stage IA adeno-carcinoma. All lung cancers were retrospectively visible as GGNs in earlier screening rounds. The lung cancer survival rate of participants with a baseline or new part-solid nodule was 100% (median follow-up after baseline 89 months).

In the largest randomized-controlled lung cancer screening trial worldwide, the National Lung Screening Trial (NLST), at least one subsolid nodule (GGN and part solid not further specified) at baseline or follow-up screening (1 and 2 years after baseline) was detected in 9.4% of participants.[8] In that study, no distinction was made between baseline subsolid nodules and newly detected in incident screening rounds. A retrospective analysis on lung cancers detected in NLST participants with a positive baseline screen result showed an odds-ratio of 0.24 for lung cancer death for cancers arising from GGNs as compared to solid nodules.[9]

The percentage subsolid nodules as reported by the NLST is much higher than the subsolid nodule prevalence reported in the largest European lung cancer screening study, the Dutch-Belgian randomized controlled lung cancer screening (acronym: NELSON) trial, in which 3.3% of participants were diagnosed with a subsolid nodule (234 participants) during either baseline screening or one of the three incidence screening rounds (1, 3, and 5.5 years after baseline).[10] Lung cancer in all resected subsolid nodules has been diagnosed in stage I, apart from one invasive adenocarcinoma (stage IV, delayed resection because of a competing malignancy). During follow-up, none of the nonresected subsolid nodules progressed into a clinical relevant malignancy. Therefore, it was concluded that even bi-annual follow-up instead of immediate resection may be a safe option in the management of subsolid nodules. Also, in this study, no differentiation was made between baseline and new subsolid nodules or between GGNs and part-solid nodules.[10]

In the Multicentric Italian Lung Detection (MILD) trial, 56/ 1866 participants (3.0%) had 76 subsolid nodules at baseline (48 GGNs, 28 part solid).[11] A quarter of the subsolid

nodules resolved spontaneously and the majority of nodules remained stable. Five percent of the subsolid nodules were diagnosed as early stage adenocarcinoma after an active surveillance approach. To the best of our knowledge, data on new subsolid nodules detected in incidence screening rounds of the MILD trial have not been published.

Guidelines on subsolid nodules detected in daily clinical practice and in screening

Subsolid nodules not only are a regular finding in lung cancer screening participants, they are often incidentally detected in asymptomatic patients as well. Two commonly used guidelines on the management of incidentally detected subsolid nodules come from the Fleischner Society and the BTS.[4,12] Lung-RADS is used for the management of screen-detected subsolid nodules.[5] Issues in the classification of subsolid nodules comprise accurate differentiation between solid, part solid, and GGNs by the radiologist,[13] and subsolid nodule size and growth determination. In contrast to measurements of solid nodules, software for semi-automated volume determination often fails measuring subsolid nodule's size. Therefore, subsolid nodule's size and growth determination are usually based on diameter measurements.

Fleischner Society

For clinical practice, the Fleischner Society recommends that solitary GGNs <6 mm do not generally require routine follow-up; however, for GGNs close to 6 mm follow-up at 2 and 4 years may be reasonable when considering nodule morphology or other risk-factors.[12] GGNs ≥6 mm should receive a follow-up within 6 to 12 months to confirm persistence and repeat scans subsequently every 2 years until 5 years follow-up. For part-solid nodules, the Fleischner Society recommends that nodules <6 mm do not necessitate routine follow-up, while nodules ≥6 mm should receive a follow-up within 3–6 months and annual LDCTs for 5 years. Persistent part-solid nodules with a solid component ≥6 mm are considered highly suspicious for lung cancer. In case of multiple subsolid nodules, management is recommended to be based on the most suspicious nodule, and in case of multiple nodules <6 mm a follow-up LDCT within 3–6 months is advised.

BTS guidelines

The current BTS guidelines do not distinguish GGNs and part-solid nodules.[4] Generally, subsolid nodules <5 mm are not recommended to receive routine follow-up. For subsolid nodules ≥5 mm it is recommended to perform a repeat LDCT within 3 months if no previous imaging exists. If unchanged, the Brock risk prediction tool is recommended to estimate the risk of malignancy.[14] Subsolid nodules with a low lung cancer risk (<10%) should receive follow-up LDCTs at 1, 2, and 4 years, while higher lung cancer risk may require diagnostic work-up. In case of growth or changes in morphology an aggressive diagnostic work-up is advised.

Lung-RADS

In Lung-RADS, management of screen-detected baseline and new GGNs/new part-solid nodules is distinguished.[5] Short-term follow-up LDCTs (3 or 6 months, lung cancer probability 1–15%) is advised for all GGNs with diameter >20 mm and part-solid nodules with diameter >6 mm (part-solid and nonsolid component combined) or any new part-solid nodule with solid component <4 mm at incident screening. More stringent follow-up using chest CT with or without contrast, PET-CT (when there is a ≥ 8mm solid component) or tissue sampling is recommended in case of a new or growing part-solid nodule with solid component ≥4 mm or a baseline part-solid nodule with solid component ≥8 mm.

Conclusion

Only limited information is available on the prevalence and lung cancer probability of subsolid nodules newly detected after baseline lung cancer screening. It remains unknown whether these results are comparable to new subsolid nodules in a European population, in which prevalence of subsolid nodules seems significantly lower. Nevertheless, current available evidence shows that malignant nonsolid nodules in baseline and new nodules typically have an indolent course and can be generally managed with follow-up by 1 or 2 years to identify nodule growth or increase in attenuation as a sign suspicious for invasive carcinoma, rather than immediate resection.

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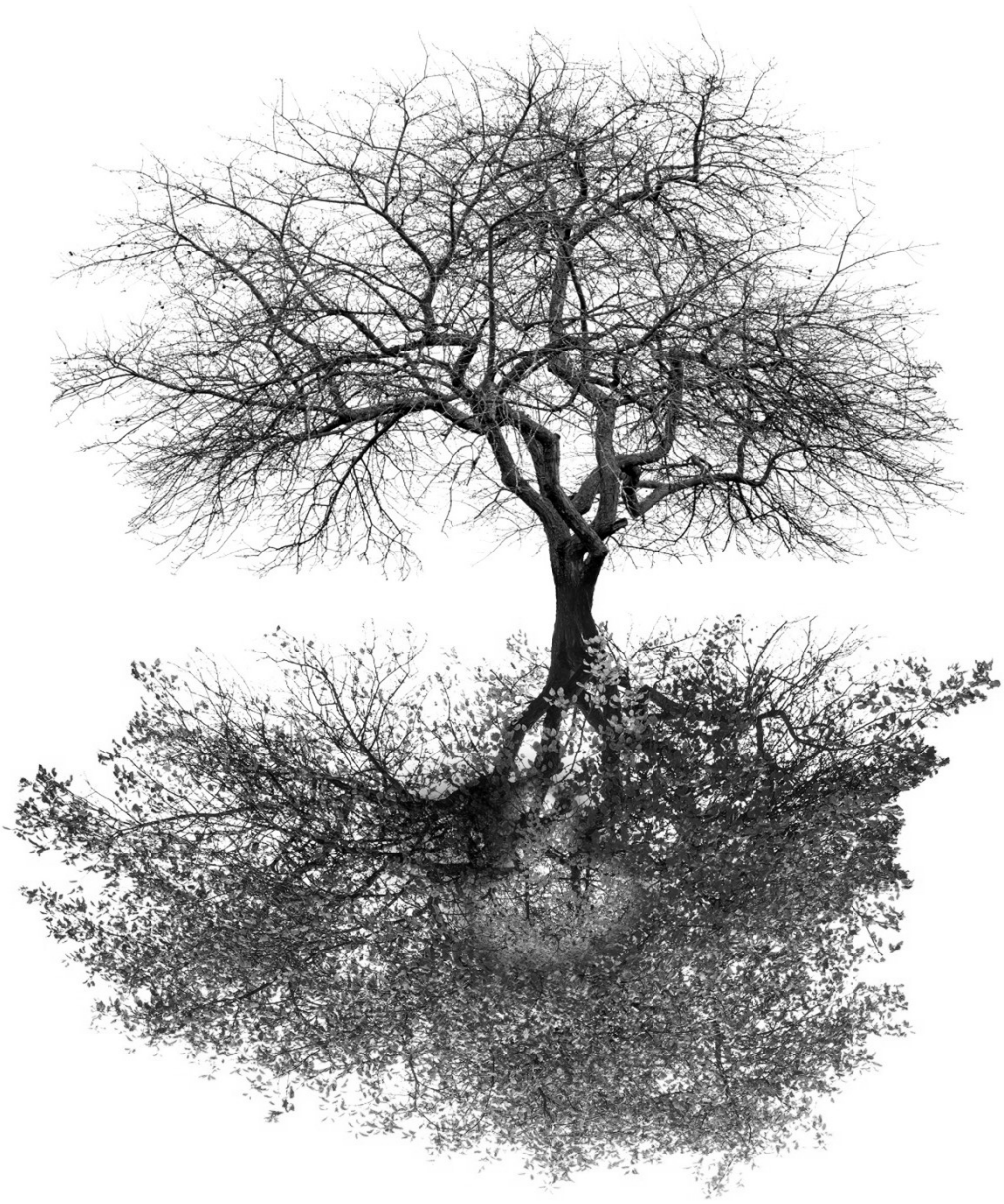
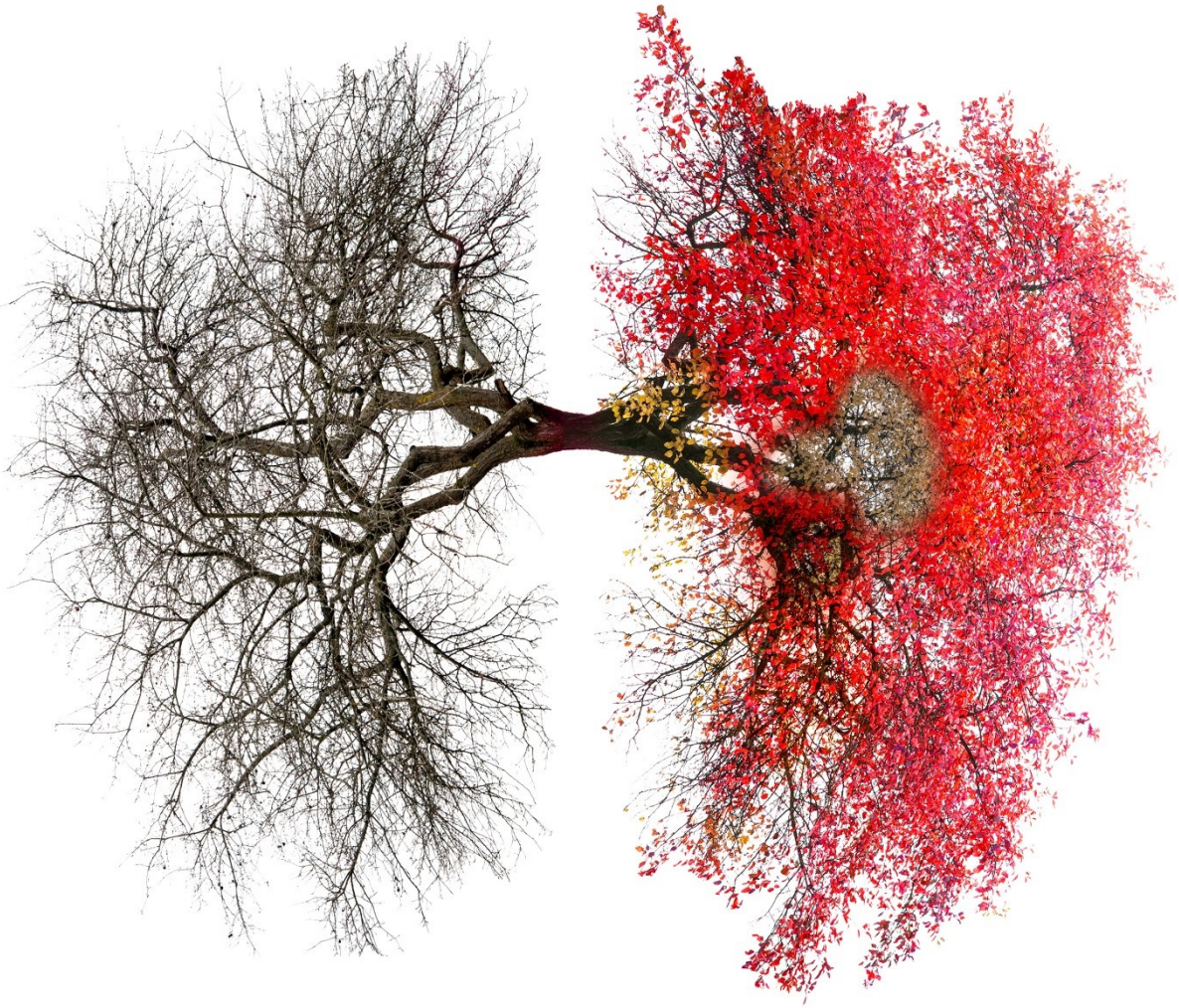


Part II
Risk-stratification of New Nodules



Chapter 4

Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT

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ABSTRACT

Background: US guidelines now recommend lung cancer screening with low-dose CT for high-risk individuals. Reports of new nodules after baseline screening have been scarce and are inconsistent because of differences in definitions used. We aimed to identify the occurrence of new solid nodules and their probability of being lung cancer at incidence screening rounds in the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON).

Methods: In the ongoing, multicentre, randomised controlled NELSON trial, between Dec 23, 2003, and July 6, 2006, 15 822 participants who had smoked at least 15 cigarettes a day for more than 25 years or ten cigarettes a day for more than 30 years and were current smokers, or had quit smoking less than 10 years ago, were enrolled and randomly assigned to receive either screening with low-dose CT (n=7915) or no screening (n=7907). From Jan 28, 2004, to Dec 18, 2006, 7557 individuals underwent baseline screening with low-dose CT; 7295 participants underwent second and third screening rounds. We included all participants with solid non-calcified nodules, registered by the NELSON radiologists as new or smaller than 15 mm^3 (study detection limit) at previous screens. Nodule volume was generated semiautomatically by software. We calculated the maximum volume doubling time for nodules with an estimated percentage volume change of 25% or more, representing the minimum growth rate for the time since the previous scan. Lung cancer diagnosis was based on histology, and benignity was based on histology or stable size for at least 2 years. The NELSON trial is registered at trialregister.nl, number ISRCTN63545820.

Findings: We analysed data for participants with at least one solid non-calcified nodule at the second or third screening round. In the two incidence screening rounds, the NELSON radiologists registered 1222 new solid nodules in 787 (11%) participants. A new solid nodule was lung cancer in 49 (6%) participants with new solid nodules and, in total, 50 lung cancers were found, representing 4% of all new solid nodules. 34 (68%) lung cancers were diagnosed at stage I. Nodule volume had a high discriminatory power (area under the receiver operating curve 0.795 [95% CI 0.728-0.862]; p<0.0001). Nodules smaller than 27 mm^3 had a low probability of lung cancer (two [0.5%] of 417 nodules; lung cancer probability 0.5% [95% CI 0.0-1.9]), nodules with a volume of 27 mm^3 up to 206 mm^3 had an

intermediate probability (17 [3.1%] of 542 nodules; lung cancer probability 3.1% [1.9-5.0]), and nodules of 206 mm(3) or greater had a high probability (29 [16.9%] of 172 nodules; lung cancer probability 16.9% [12.0-23.2]). A volume cutoff value of 27 mm^3 or greater had more than 95% sensitivity for lung cancer.

Interpretation: Our study shows that new solid nodules are detected at each screening round in 5-7% of individuals who undergo screening for lung cancer with low-dose CT. These new nodules have a high probability of malignancy even at a small size. These findings should be considered in future screening guidelines, and new solid nodules should be followed up more aggressively than nodules detected at baseline screening.

Introduction

Lung cancer is a leading cause of death worldwide.[1] Randomised controlled trials of lung cancer screening in Europe and the USA have explored the value of low-dose CT in detection of lung cancer at an early stage to improve prognosis.[2,3] The National Lung Screening Trial showed a relative reduction in lung cancer mortality of 20% with low-dose CT compared with chest radiography.[4] In view of these results, most US guidelines now recommend lung cancer screening with low-dose CT for high-risk individuals.[5–12]

So far, most research has focused on lung nodules detected during baseline screening. However, new nodules can be detected at subsequent screening rounds and complicate management.[13] Reports of new nodules have been inconsistent because of differences in definitions of incident nodules, which restricts comparability.[7] New nodule and respective cancer rates are seldom reported explicitly, and are difficult to deduce from published results. In 2005, the Fleischner Society, referring to Swensen and colleagues' Mayo Clinic trial, suggested that 10% of screening participants will develop a new nodule annually.[14,15] On the basis of results from the Early Lung Cancer Action Project (ELCAP),[16] the International-ELCAP (I-ELCAP),[17] the Pittsburgh Lung Screening Study (PLuSS),[13] and the Mayo trial, an estimated 3.4–13.1% of screening participants develop a new nodule each year.[15] Because these nodules developed within a short time-interval, they are expected to be fast growing. This factor differentiates new nodules from those detected at baseline, which might have been present for years. Lung cancers found in incidence screening rounds tend to be more aggressive than those detected at baseline.[18–20] Data from the ELCAP, I-ELCAP, and Mayo trials show that between 1.6% and 7.5% of participants with new nodules develop lung cancer in such a nodule.[15–17]

These results suggest that new lung nodules, although mostly benign, might have a higher probability of being lung cancer than do nodules detected at baseline. Nevertheless, little is known about lung cancer probability and new nodule volume at initial detection, or about lung cancer characteristics of new nodules, including histology and stage distribution. Up to now, no study has focused on new solid nodules found during lung cancer screening.

We did this analysis to assess the occurrence of new solid nodules and their lung cancer probability, and to compare the volume of malignant and benign new solid

nodules at initial detection in incidence screening rounds of the Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON).

Methods

Study design and participants

The recruitment process and study design of the NELSON trial have been previously published and are described in the appendix (pp 1, 2).[21–23] Briefly, between Dec 23, 2003, and July 6, 2006, 15 822 participants from four centres in the Netherlands and Belgium were enrolled and randomly assigned to receive low-dose CT screening (n=7915) or no screening (n=7907). Eligible patients were adults aged 50–75 years, who had smoked 15 or more cigarettes per day for more than 25 years or ten or more cigarettes per day for more than 30 years, and were still smoking or had stopped smoking less than 10 years previously. People with self-reported moderate or bad health (with a questionnaire adapted from the SF-36 questionnaire), inability to climb two flights of stairs, bodyweight of 140 kg or more, current or past renal cancer, melanoma, breast cancer, or lung cancer diagnosed less than 5 years ago, or a chest CT examination less than 1 year ago, were excluded.

From Jan 28, 2004, to Dec 18, 2006, 7557 participants underwent baseline screening.[23] The second screening round took place 1 year after the baseline scan (annual screen) and the third screening round took place

2 years after the second screening scan (biannual screen). Results of the fourth screening round, done 5.5 years after baseline (2.5 year screening interval), have not yet been published, and were not included in the present analysis.

For our study, we included all participants with a solid non-calcified nodule in the second or third screening round, registered by the NELSON radiologists as new or smaller than 15 mm³ (study detection limit)[24] at previous screens. Nodules not registered as new, such as previously missed nodules, were excluded. The NELSON trial was approved by Ethics Committees of all participating centres in the Netherlands and Belgium, and authorised by the Dutch Health Care Committee. All participants gave written informed consent.

Procedures

The CT scan protocol of the NELSON trial has been previously published.[21,23] At all screening sites, 16-multidetector CT scanners or, in later rounds, 64-multidetector scanners were used (Sensation-16 or Sensation-64, Siemens Medical Solutions, Forchheim, Germany; or Mx8000 IDT, Brilliance 16P, or Brilliance 64, Philips Medical Systems, Best, Netherlands). Reconstructions were made with 1.0-mm slice width and 0.7-mm interval. Screening conditions and data acquisition were standard across screening sites.[21,23]

In the first two screening rounds, CT scans were read by at least two independent radiologists with experience in thoracic CT ranging from 1 year to more than 20 years. In the third and fourth screening rounds, single reading was done by radiologists with at least 6 years of experience in thoracic imaging. CT data analysis was done on digital workstations (Leonardo, Siemens Medical Solutions, Forchheim, Germany) with semiautomated volumetric software (LungCARE, version Somaris/5 VA70C-W, Siemens Medical Solutions, Forchheim, Germany). On the basis of the three-dimensional nodule volume, this software also simulated longest and perpendicular nodule diameter in the axial plane. Within the NELSON nodule management protocol, radiologists could over-rule protocol-based screening results (done for 195 [6%] of 3318 participants at the baseline screening round).[25] High suspicion of malignancy (eg, enlarged mediastinal lymph nodes) or benignity (eg, benign calcification patterns) were reasons for manual adjustment.[25]

For subsequent CT scans, nodules were individually matched on previous scans by the software's matching algorithm (depending on consistency, size, and location), and visually checked by the radiologists. Nodules were classified as new if they were not present or smaller than the detection limit (<15 mm³) at any previous scan.[21] Exact volumes of nodules smaller than 15 mm³ at initial detection or at retrospective assessment were not recorded in the database. Data generated during CT evaluation were immediately uploaded to the NELSON management system.[21] For our study, we used nodule information at first nodule detection as reported in the NELSON management system. For nodules eventually diagnosed as cancer, we supplemented data with cancer-specific information obtained at diagnosis, such as histology and stage. We included only screen-detected lung cancers in this analysis because interval cancers of the NELSON trial's first three rounds have been reported previously.[26]

The NELSON nodule management protocol has been described in detail elsewhere and is summarised in the appendix (pp 1, 2).[21] In brief, the screening outcome could be negative (regular screening continued), indeterminate (short-term follow-up low-dose CT), or positive (immediate referral to pulmonologist). At first detection (baseline or incidence screening), solid nodules were assessed based on volume. Because new nodules were considered fast-growing, their follow-up strategy differed from baseline nodules.[21] New nodules measuring 15–50 mm³ without benign characteristics were considered indeterminate (follow-up low-dose CT after 1 year), new nodules measuring 50–500 mm³ were also considered indeterminate (follow-up low-dose CT within 6–8 weeks), and new nodules measuring 500 mm³ or more were considered positive (immediate referral to pulmonologist). After initial detection, subsequent evaluation of a nodule was based on growth and volume doubling time. Growth was defined as a percentage volume change of 25% or more, and led to calculation of the volume doubling time as described in the nodule management protocol.[21]
In case of positive screening results, participants were referred for diagnostic work-up according to national and international guidelines.[21,27] Malignancy was based on histology, and benignity was based on histology or stable size for at least 2 years.[21] The NELSON chief pathologist reassessed obtained lung cancer specimens.[27]

Statistical analysis

At initial detection of a new solid nodule after baseline screening, regular calculation of the volume doubling time is impossible because no earlier measurement is available for comparison. For our analysis, we estimated a maximum volume doubling time, representing the minimum growth rate for the time since the previous scan, with the formula:

$$VDT^{max}(days) = \frac{[ln2 \times \Delta t]}{[ln\,(V2/V1)]}$$

where VDT_{max} is the maximum volume doubling time, V2 is the volume of the new nodule at first detection, V1 is the study detection limit of 15 mm³ as maximum volume at the previous scan, and Δt is the time between new solid nodule detection and previous scan in days. We calculated the maximum volume doubling time for nodules with an estimated percentage volume change of 25% or more (≥18.75 mm³),

considering 15 mm³ as V1. In theory, the actual volume doubling time in the examined time interval might have been faster, but not slower, than the calculated maximum time.

Normality testing for continuous variables was done with the Kolmogorov–Smirnov test. Continuous variables were analysed with the Mann–Whitney U test and are presented as medians and IQRs. We used Fisher's exact test to analyse nominal variables. We calculated 95% CIs with the Agresti–Coull method. We calculated probabilities of lung cancer stratified by different nodule variables by dividing the number of lung cancers by the total number of nodules. Receiver operating characteristic (ROC) analysis was done for nodule volume and simulated mean nodule diameter (mean of longest and perpendicular simulated diameter) at first new nodule detection with eventual lung cancer diagnosis as the outcome to evaluate their performance as predictors of lung cancer and to estimate cutoff values. We derived cutoff values with a predefined overall sensitivity of 95% and Youden Indices as reference points for further adaption,[28] optimising intermediate and high-risk groups. Appendix p 2 describes the calculations used for ROC analysis for participant-level calculations. We calculated sensitivities by dividing true-positive cases by the numbers of true-positive and false-negative cases. We calculated specificities by dividing true-negative cases by the numbers of true-negative and false-positive cases. We developed a risk prediction model to assess whether the established relation between volume of a new solid nodule and lung cancer diagnosis remained significant independent of other risk factors (ie, age, sex, pack-years, smoking status, time since previous scan, solid nodule count at baseline, and nodule imaging and volume; appendix p 4). All statistical tests were two-sided and $p<0.05$ was deemed significant. We did statistical analysis with SPSS (version 22), R (version 3.2.3), and Microsoft Excel (2010). The NELSON trial is registered with trialregister.nl, number ISRCTN63545820.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JEW, MAH, RV, and HJdK had access to the raw data. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Figure 1 shows a flowchart of new solid nodules detected within the second and third screening round.

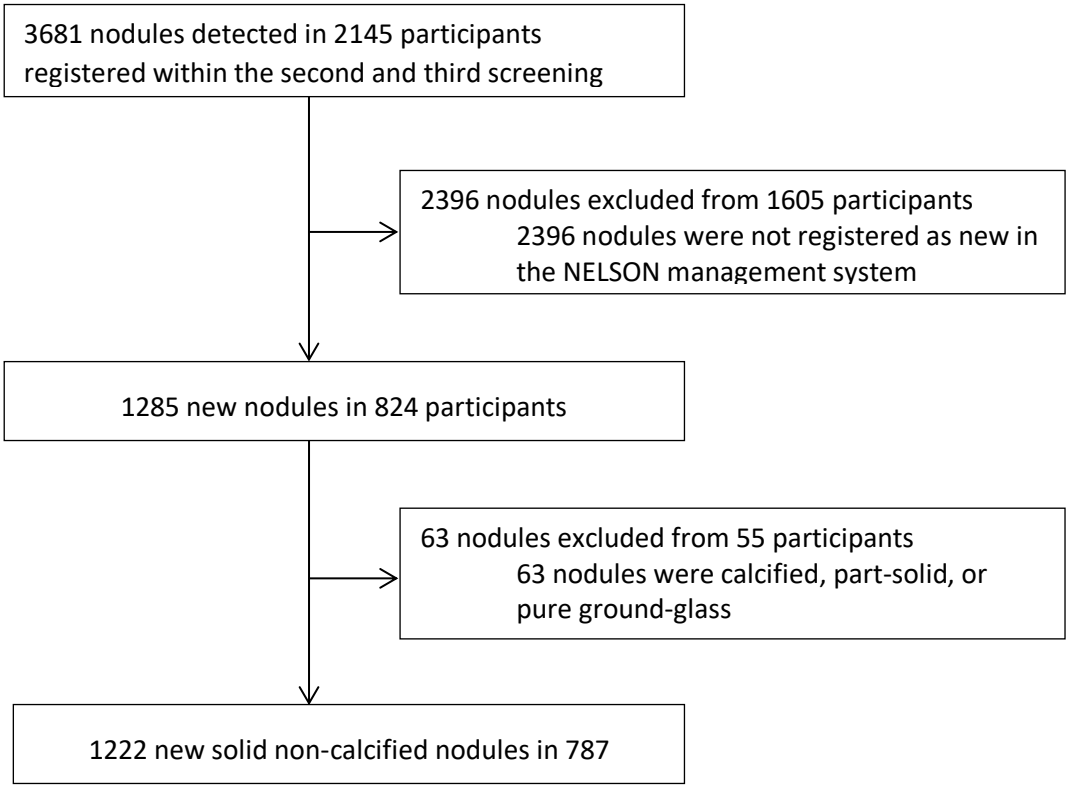

Figure 1: Flowchart of new solid nodules detected during the second and third screening rounds
Some participants had a new nodule and, for example, previously missed nodules. Whereas the missed nodule was excluded, the new nodule (and therefore the participant) was included

Of the 15 822 participants enrolled in the NELSON trial, 7907 (50%) participants were assigned to the no screening group; 620 (8%) of 7915 screening participants did not participate in the second screening examination for various reasons (eg, lung cancer diagnosis at baseline, death, dropout); 5150 (71%) of 7295 participants in the second and third screening rounds had no new nodule described and, in 1605 (75%) of 2145 participants with new nodules described, a nodule was not identified as new by the radiologist (eg, missed at previous screen), excluding 1321 (18%) participants without a new nodule; and 37 (<1%) participants with only calcified or subsolid new nodules were not included. 1222 new solid nodules were registered in 787 (11%) of the 7295 participants who underwent second and third screening scans (not accounting for participant dropout; figure 1). 273 (22%) of new solid nodules represented nodules

retrospectively identified as smaller than the detection limit (<15 mm³) in a previous screen. limit (<15 mm³) in a previous screen.

Table 1 shows characteristics of included participants.

	Overall (N=787)	Lung cancer		p value
		Yes (n=49)	No (n=738)	
Sex				0.12
Female	186 (24%)	7 (14%)	179 (24%)	
Male	601 (76%)	42 (86%)	559 (76%)	
Age (years)				0.20
<50	1 (<1%)	0	1 (<1%)	
50–54	180 (23%)	12 (24%)	168 (23%)	
55–59	237 (30%)	10 (20%)	227 (31%)	
60–64	216 (27%)	13 (27%)	203 (28%)	
65–69	103 (13%)	10 (20%)	93 (13%)	
≥70	50 (6%)	4 (8%)	46 (6%)	
Median (IQR)	59 (55–63)	61 (55–65)	59 (55–63)	
Smoking pack-years*				0.013
<20	2/786 (<1%)	0	2/737 (<1%)	
20–39	431/786 (55%)	19 (39%)	412/737 (56%)	
40–59	245/786 (31%)	16 (33%)	229/737 (31%)	
60–79	73/786 (9%)	10 (20%)	63/737 (9%)	
≥80	35/786 (4%)	4 (8%)	31/737 (4%)	
Median (IQR)	38.7 (29.7–49.5)	43.7 (31.7–61.5)	38.7 (29.7–49.5)	
Solid baseline nodules†				0.038
0	359 (46%)	29 (59%)	330 (45%)	
1	190 (24%)	11 (22%)	179 (24%)	
2	108 (14%)	4 (8%)	104 (14%)	
3	42 (5%)	1 (2%)	41 (6%)	
≥4	88 (11%)	4 (8%)	84 (11%)	
Median (IQR)	1 (0–2)	0 (0–1)	1 (0–2)	

Data are n (%) or n/N (%), unless otherwise specified. *Information was missing for one participant. †Number of non-calcified solid nodules present at baseline screening.

Table 1: **Characteristics of participants with at least one new solid nodule during second or third screening**

A higher number of pack-years smoked and a lower number of solid nodules at baseline screening significantly increased the probability of a new solid nodule being

lung cancer (table 1). Increased age was not significantly associated with lung cancer (table 1). In 359 (46%) participants, no solid nodule had been found during baseline screening (table 1). In 49 (6%) participants with new solid nodules, a new solid nodule was lung cancer (table 1). One participant was diagnosed with synchronous double tumours in two new nodules. In total, 50 lung cancers were found, representing 4% of all new solid nodules (table 2).

	Second screening round*	Third screening round*	Second and third screening rounds
All participants	7295	6922	7295
Participants with new nodules	344 (5%)	491 (7%)	787 (11%)†
With new solid lung cancer	14/344 (4%)	35/491 (7%)	49/787 (6%)
New solid nodules	476	746‡	1222‡
<50 mm³	278 (58%)	419/743 (56%)	697/1219 (57%)
50–500 mm³	158 (33%)	267/743 (36%)	425/1219 (35%)
≥500 mm³	40 (8%)	57/743 (8%)	97/1219 (8%)
Lung cancer	14	36	50
<50 mm³	4 (29%)	6 (17%)	10 (20%)
50–500 mm³	6 (43%)	14 (39%)	20 (40%)
≥500 mm³	4 (29%)	16 (44%)	20 (40%)
Probability of lung cancer	14/476 (3%)	36/746 (5%)	50/1222 (4%)
95% CI	1.7–4.9	3.5–6.6	3.1–5.4
Cancer stage at diagnosis			
IA	11/14 (79%)	21/36 (58%)	32/50 (64%)
IB	0	2/36 (6%)	2/50 (4%)
IIA	1/14 (7%)	2/36 (6%)	3/50 (6%)
IIB	0	0	0
IIIA	2/14 (14%)	7/36 (19%)	9/50 (18%)
IIIB	0	1/36 (3%)	1/50 (2%)
IV	0	0	0
Not specified	0	3/36 (8%)	3/50 (6%)
Time of referral§			
Immediately	5/14 (36%)	19/36 (53%)	24/50 (48%)
Follow-up	6/14 (43%)	12/36 (33%)	18/50 (36%)
Subsequent round	3/14 (21%)	5/36 (14%)	8/50 (16%)

Data are n/N (%) or n (%), unless otherwise specified. 50 lung cancer nodules were detected in 49 participants. *Incidence screenings 1 year (second screening round; annual screen) and 3 years (third screening round; biannual screen) after baseline screening. †48 participants developed new solid nodules in both incidence rounds, but were accounted for only once in the total number of participants with new nodules. ‡Size categorisation was missing for three benign nodules. §Referral to pulmonologist for work-up and diagnosis.

Table 2: **New solid new nodules detected during second and third screening rounds (N=1222; 1172 benign nodules and 50 lung cancer nodules)**

Median nodule size at first detection of new solid nodules was 41 mm³ (IQR 21–116), and median volume of lung cancers (296 mm³ [IQR 73–721]) differed significantly from benign nodules (39 mm³ [21–103]; p<0.0001). ROC analysis showed an area under the curve (AUC) for nodule volume of 0.795 (figure 2). However, the value of nodule size as predictor for lung cancer differed with varying screening interval length; in the second screening round nodule volume had an AUC of 0.686, whereas the AUC rose in the third screening round to 0.837 (figure 2).

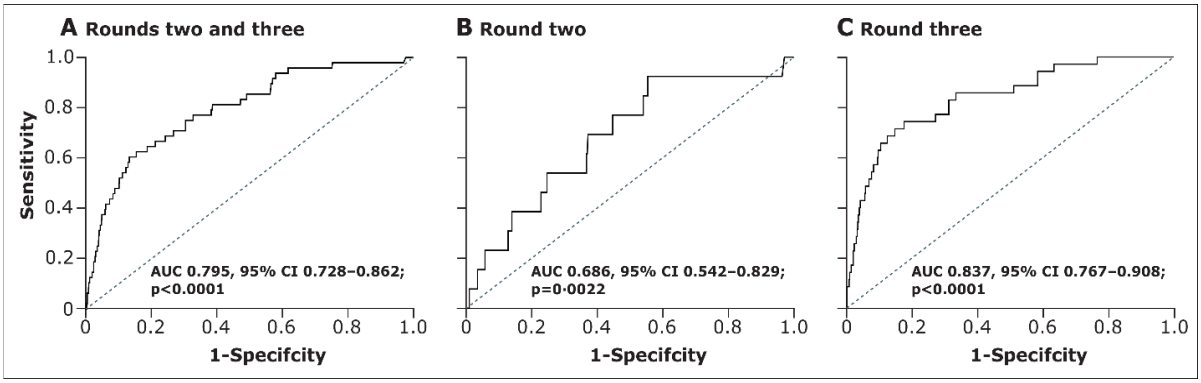

Figure 2: Receiver operating characteristic curves of nodule volume at initial detection, discriminating malignant from benign new solid nodules

Exact volume measurement was not available for 89 benign nodules and two cancers, and they were not included in the calculations. AUC=area under the curve.

In the NELSON trial, the volume cutoff value for new nodules, leading to follow-up within 6–8 weeks, was 50 mm³ or more, which provided a sensitivity of 81.3% (95% CI 67·8–90·0) and a specificity of 57.7% (54.7–60.6) for lung cancer. To reach 95% sensitivity, a cutoff value of 27 mm³ or more (sensitivity 95.8% [95% CI 85.2–99.6]; specificity 38.3% [35.5–41.3]) would be necessary. Nodules smaller than 27 mm³ had a low lung cancer probability, nodules with a volume of 27 mm³ up to 206 mm³ had an intermediate probability, and nodules of 206 mm³ and higher had a high probability (table 3).

	Second screening round (lung cancer/ total nodules)	Third screening round (lung cancer/total nodules)	Second and third screening rounds (lung cancer/ total nodules)	Lung cancer probability (95% CI)
New solid nodules	13/452 (3%)	35/679 (5%)	48/1131 (4%)	4.2% (3.2–5.6)
<25 mm³	1/160 (1%)	1/216 (<1%)	2/376 (1%)	0.5% (0.0–2.0)
25 to <50 mm³	3/104 (3%)	4/154 (3%)	7/258 (3%)	2.7% (1.2–5.6)
50 to <100 mm³	2/72 (3%)	4/113 (4%)	6/185 (3%)	3.2% (1.3–7.1)
100 to <200 mm³	2/46 (4%)	2/85 (2%)	4/131 (3%)	3.1% (0.9–7.8)
200 to <300 mm³	2/19 (11%)	4/31 (13%)	6/50 (12%)	12.0% (5.2–24.2)
300 to <400 mm³	0/14	2/18 (11%)	2/32 (6%)	6.3% (0.7–21.2)
400 to <500 mm³	0/8	3/20 (15%)	3/28 (11%)	10.7% (2.9–28.0)
≥500 mm³	3/29 (10%)	15/42 (36%)	18/71 (25%)	25.4% (16.6–36.6)
Cutoff values				
<27 mm³	1/180 (1%)	1/237 (<1%)	2/417 (<1%)	0.5% (0.0–1.9)
27 to <206 mm³	7/206 (3%)	10/336 (3%)	17/542 (3%)	3.1% (1.9–5.0)
≥206 mm³	5/66 (8%)	24/106 (23%)	29/172 (17%)	16.9% (12.0–23.2)

Data are n/N (%), unless otherwise specified. Exact volume measurement was not available for 89 benign nodules and two cancers, and they were not included in the calculations.

***Table 3*: Volume at first detection and lung cancer probability of new solid nodules (N=1131; 1083 benign nodules and 48 lung cancer nodules)**

On the basis of the simulated mean diameter, proposed cutoff values are smaller than 3.7 mm for a negative screen (≥3.7 mm: sensitivity 95.8% [95% CI 85.2–99.6]; specificity, 32.9% [30.2–35.8]), and 8.2 mm or more for a positive screen (appendix p 3).

The median maximum volume doubling time of new nodule lung cancers differed significantly from the median time of benign new nodules (139 days [IQR 104–211] vs 278 days [140–549]; p<0.0001;

appendix p 3). The median maximum volume doubling time of adenocarcinomas was 191 days (IQR 146–348) and of squamous-cell carcinomas was 133 days (105–182; table 4).

	Total	Histological type								
		AdC	SqCC	AdSqLC	LCLC	LCNEC	SCLC	NSCLC/SCLC	NSCLC-NOS	Unknown*
Overall	50 (100%)	19 (38%)	11 (22%)	1 (2%)	4 (8%)	1 (2%)	5 (10%)	1 (2%)	1 (2%)	7 (14%)
Volume at first detection										
<50 mm³	10 (20%)	8 (42%)	1 (9%)	0	0	0	0	0	0	1 (14%)
50–500 mm³	20 (40%)	8 (42%)	3 (27%)	0	4 (100%)	1 (100%)	1 (20%)	0	1 (100%)	2 (29%)
≥500 mm³	20 (40%)	3 (16%)	7 (64%)	1 (100%)	0	0	4 (80%)	1 (100%)	0	4 (57%)
Median (IQR)	296 (73–721)	97 (32–370)	658 (96–959)	NA†	157 (68–226)	212 (NC‡)	2373 (661–3108)	3482 (NC‡)	299 (NC‡)	580 (82–1108)
Simulated mean diameter (mm)§	9.3 (5.2–14)	5.8 (4.6–11.1)	12.9 (6.8–17.5)	NA†	7.3 (5.4–8.9)	8.2 (NC‡)	19.8 (14.8–20.7)	19.6 (NC‡)	12.6 (NC‡)	11.6 (5.3–13.7)
Estimated volume doubling time (days)	139 (104–211)	191 (146–348)	133 (105–182)	NA†	117 (90–191)	161 (NC‡)	82 (36–96)	101 (NC‡)	169 (NC‡)	124 (69–328)
Stage at diagnosis										
IA	32 (64%)	15 (79%)	7 (64%)	0	3 (75%)	1 (100%)	0	0	1 (100%)	5 (71%)
IB	2 (4%)	2 (11%)	0	0	0	0	0	0	0	0
IIA	3 (6%)	0	1 (9%)	1 (100%)	0	0	0	0	0	1 (14%)
IIB	0	0	0	0	0	0	0	0	0	0
IIIA	9 (18%)	1 (5%)	3 (27%)	0	1 (25%)	0	3 (60%)	1 (100%)	0	0
IIIB	1 (2%)	1 (5%)	0	0	0	0	0	0	0	0
IV	0	0	0	0	0	0	0	0	0	0
Not specified	3 (6%)	0	0	0	0	0	2 (40%)	0	0	1 (14%)
Time of referral										
Immediately	24 (48%)	3 (16%)	9 (82%)	1 (100%)	1 (25%)	0	5 (100%)	1 (100%)	0	4 (57%)
Follow-up	18 (36%)	10 (53%)	2 (18%)	0	3 (75%)	1 (100%)	0	0	0	2 (27%)
Subsequent round	8 (16%)	6 (32%)	0	0	0	0	0	0	1 (100%)	1 (14%)

Data are n (%) or median (IQR), unless otherwise specified. AdC=adenocarcinoma. SqCC=squamous-cell carcinoma. AdSqLC=adenosquamous lung carcinoma. LCLC=large-cell lung carcinoma. LCNEC=large-cell neuroendocrine carcinoma. SCLC=small-cell lung cancer. NSCLC/SCLC=mixed non-small-cell lung carcinoma and small-cell lung cancer. NSCLC-NOS=non-small-cell lung carcinoma not otherwise specified. NA=not available. NC=not calculable. *Histological diagnosis could not be established. †No exact volume measurement was available and no simulated mean diameter was generated. ‡Too few nodules available for calculation. §Diameters were simulated from computer-generated volume measurements, based on three-dimensional voxels. Manually measured diameters are less accurate and will overestimate nodule size.

Table 4: **Lung cancer characteristics of new solid nodules**

However, in this analysis maximum volume doubling time did not improve risk stratification by nodule volume (data not shown). The median maximum volume doubling time of new nodule lung cancers did not differ significantly between the second and the third screening rounds (127 days [IQR 73–206] vs 144 days [105–220]; p=0.48).

Less than half of screen-detected lung cancers in new solid nodules were 500 mm³ or more at first nodule detection (table 4). Histologically, most lung cancers were adenocarcinomas, squamous-cell carcinomas, or small-cell lung carcinomas (table 4). Most small-cell lung carcinomas and squamous-cell carcinomas had volumes greater than 500 mm³ at first nodule detection (table 4). However, few adenocarcinomas initially presented with volumes of 500 mm³ and more, whereas roughly two-fifths were smaller than 50 mm³ at first detection. Most lung cancers were diagnosed at stage I (table 4). Of cancers detected in the second screening round, 11 (79%) of 14 were stage I, compared with 23 (64%) of 36 in the third screening round (p=0.50; table 2). In about half the lung cancer cases, participants were referred immediately after first new solid nodule detection (table 4). Adenocarcinomas tended to be referred later,

with 16 (84%) of 19 nodules not being referred immediately, whereas only ten (32%) of the other 31 cancers were not referred immediately (p=0.00045; table 4).

Discussion

In this study, we determined the occurrence of solid nodules newly detected in the second or third screening round of the NELSON trial, assessed their lung cancer probability, and provided information about stage and cancer histology. Furthermore, we proposed cutoff values for nodule volume as a guide for further management of new solid nodules in lung cancer screening. In the first two incidence screening rounds of the NELSON trial, radiologists registered new solid nodules in 787 (11%) of 7295 participants. A new solid nodule was diagnosed as lung cancer in 49 (6%) of 787 participants. Most lung cancers were adenocarcinoma, squamous-cell carcinoma, and small-cell lung cancer, and most were diagnosed at stage I. Nodule volume could be used for risk stratification in new solid nodules, with a sensitivity of more than 95% for a volume cutoff of 27 mm³ or more. In this setting, new solid nodules of 206 mm³ or more had a high lung cancer probability.

Few studies of lung cancer screening have published detailed data regarding new nodules at incidence screening rounds. As stated in British Thoracic Society guidelines[29] for the investigation and management of pulmonary nodules, little evidence exists for the management of new nodules that appear in follow-up CTs. Our study not only offers insight into the cancer probability of such nodules, but also provides information about stage and cancer histology. Furthermore, to our knowledge, this is the first time nodule volume cutoff values have been established as a guide for further management of new solid nodules in lung cancer screening.

In the second screening round, 344 (5%) of 7295 participants had new solid nodules. This number is somewhat similar to annual new nodule numbers reported in the I-ELCAP trial (1460 [5%] of 27 456 participants), the ELCAP trial (40 [3%] of 1184 participants), and the PluSS trial (256 [7%] of 3423 participants);[13,16,17] the Mayo Clinic trial reported a higher proportion (191 [13%] of 1464 participants).[15] Nevertheless, these data are restricted in their comparability, because new nodules were defined differently within trials and rates of new nodule detection have not been reported explicitly.[7]

The clinical significance of new solid nodules is underlined by the high cancer rate. In the NELSON trial, 70 (1%) of 7557 participants were found to have lung cancer during baseline screening,[23] and 200 (3%) of 7582 participants were found to have lung cancer during the first three screening rounds.[27] Nevertheless, cancers detected in the first three rounds include those found within 44 participants with new nodule lung cancer (excluding five participants in whom cancer diagnosis occurred in the fourth round). In the present study, a new solid nodule was lung cancer in 6% of participants with new solid nodules. When these numbers are compared, new solid nodules seem to have a higher lung cancer probability than do baseline nodules. Furthermore, at baseline, 3816 (50%) of 7557 participants had at least one pulmonary nodule, causing further follow-up in 1570 (21%) participants due to suspiciousness of a nodule.[23] Eventually, lung cancer was found in 80 (5%) of 1570 participants with an indeterminate or positive test result at baseline.[23] In that sense, mere detection of a new solid nodule during incidence screening might carry the same lung cancer probability as a suspicious test result during baseline screening (6% vs 5%; p=0.25).

In 2014, the American College of Radiologists released assessment categories for nodules detected during lung cancer screening (so-called Lung-RADS) and, as in the NELSON nodule management protocol, follow-up for new nodules is recommended at smaller sizes than for baseline nodules.[21,30] Our results confirm that new solid nodules detected during incidence rounds of lung cancer screening need a more aggressive follow-up strategy than baseline nodules, with short-term follow-up evaluation for growth assessment required for smaller nodules. At these tiny nodule sizes, growth detection based on two-dimensional diameter evaluation is unreliable,[31] favouring volumetry.

In the NELSON trial, baseline nodules smaller than 100 mm³ had a lung cancer probability of about 0.6%, were not predictive of lung cancer, and did not necessitate additional follow-up scans.[32] However, this criterion does not apply in the case of new solid nodules. As shown in the present study, 3% of participants whose largest new solid nodule was smaller than 100 mm³ were eventually diagnosed with lung cancer, with 15 (1.8%) of 819 new solid nodules smaller than 100 mm³ found to be lung cancer. Large volume of new solid nodules was the most important predictor of lung cancer, and remained so after correction for possible confounding variables such as time from previous CT scan, sex, age, number of pack-years, nodule margin, solid nodule count at baseline (multinodularity), and nodule location, with a cutoff value of 27 mm³ or more

for further follow-up of new solid nodules having more than 95% sensitivity. Age was not significantly associated with new nodule lung cancer. Possible explanations could be that the number of cases was too low to show the correlation, or perhaps fast nodule growth is less associated with age, possibly even with a converse relation, with older individuals having less fast-growing nodules. We identified that new solid nodules smaller than 27 mm³ have a low lung cancer probability and their detection should be followed by regular screening, new solid nodules of 27 mm³ up to 206 mm³ have an intermediate lung cancer probability requiring short-term follow-up, and new solid nodules of 206 mm³ or greater have a high lung cancer probability necessitating immediate diagnostic evaluation. These findings could be incorporated into radiology protocols under development for new trials of lung cancer screening. Nevertheless, the proposed cutoff estimates based on the first three rounds of the Nelson trial might be adjusted when further data become available from this or other ongoing trials, such as the UK Lung Cancer Screening Trial (ISRCTN78513845). Combining trial data from NELSON and the UK Lung Cancer Screening Trial, which used the same volume screen protocols, could provide further insight into if and how lung cancer screening protocols should be improved, and might be necessary to obtain a number of cases large enough to enable even more accurate assessment.

We provided cutoff values for simulated mean nodule diameter. Nodules smaller than 3.7 mm had low lung cancer probability, nodules of 3.7 mm to less than 8.2 mm had intermediate lung cancer probability, and nodules of 8.2 mm or greater had high lung cancer probability. These probabilities are in concordance with lung cancer probabilities for the respective American College of Radiologists Lung-RADS categories.[30] However, these diameters represent simulated diameter measurements of new nodules, extrapolated from computer-generated volume measurements based on three-dimensional voxel analysis.[33] Manual diameter measurements are far less precise and reproducible,[31] and would probably yield different results.

The difference in risk stratification of nodule volume between second and third screening rounds (AUC 0.686 [95% CI 0.542–0.829] vs 0.837 [0.767–0.908]) suggests that new nodules need time to grow in order to be evaluated based on size only, making measures such as the volume doubling time crucial for follow-up assessment. Whether our results can be used to guide management of incidentally detected nodules depends on the setting in which the nodule was detected. First, a previous chest CT must be available to confirm that the nodule is actually new. Second, the

presented lung cancer probabilities were based on a high-risk population with a relatively high prevalence of lung nodules (about 50%),[32] and high overall lung cancer risk (about 3% in the first 5 years).[34] Our results and cutoffs should only be extrapolated in a population with similar nodule prevalence and lung cancer risk. Although we highly recommend separate, more stringent, guidelines for new nodules on the basis of our results, future studies based on incidentally detected nodules should focus on cutoff values for this nodule group.

Of the 50 new nodule lung cancers, 34 (68%) were stage I, which is similar to numbers recorded during baseline screening of the NELSON trial (46 [64%] of 72 cancers; p=0.70) and for overall screening in the first three rounds (148 [71%] of 209 cancers; p=0.73).[23,27] Fewer small-to-intermediate sized lung cancers (<500 mm³) were found after biannual screening than after annual screening (ten [71%] of 14 vs 20 [56%] of 36). However, the proportion of stage I cancers did not differ significantly between annual and biannual screening, although the number of cancers had roughly doubled (14 vs 36 cancers). The maximum volume doubling time was significantly lower in new nodule lung cancers than in benign new solid nodules. Notably, the median maximum volume doubling time of adenocarcinomas (191 days [IQR 146–348]) and squamous-cell carcinomas (133 days [105–182]) was similar to previously published volume doubling time of fast-growing baseline cancers in the NELSON trial of the same histological type (196 days [IQR 135–250] and 142 days [91–178], respectively).[35] Perhaps fast-growing baseline cancer and new nodule cancer represent a group of relatively young cancers. Nevertheless, even though malignant new nodules might be fast growing, detection at an early stage is possible with low-dose CT screening and use of volume doubling time for evaluation after first detection. Compared with the overall screening results of the first three rounds,[27] new solid nodule cancer comprised 11 (19%) of 58 cancers found in the second screening round (excluding three new nodule lung cancers for which diagnosis occurred in the third round) and 34 (44%) of 77 cancers even in the third screening round (excluding five new nodule lung cancers for which diagnosis occurred in the fourth round). Thus, management of new solid nodules has a great impact on the outcome of a lung cancer screening programme.

Most trials of lung cancer screening have used an annual screening algorithm. The NELSON study was designed to also study the effect of prolonged screening intervals, enabling us to provide insights into differences between annual and biannual screening. Presented cutoff values were based on new solid nodules detected after

annual and biannual screening and their respective follow-ups, which might make direct applications to an annual screening routine difficult.

Our study had some limitations. We excluded nodules smaller than 15 mm^3, because they were below the detection limit of the NELSON trial and were therefore not reported by the radiologists. We cannot exclude the possibility that the actual number of new nodules is somewhat higher than we report based on the NELSON management system information. Second, we included only solid nodules, with exclusion of part-solid and pure ground-glass nodules. Furthermore, calculation of a maximum volume doubling time for new nodules is a new and not yet validated approach, and so needs further investigation. Rates of new solid nodules and cancer differed between the incidence screening rounds. This inconsistency could be explained by the varying time intervals between screening rounds and respective follow-up examinations, and by the learning effect of radiologists. Radiologists potentially gained increased expertise in distinguishing scars or infections from suspicious lesions, and might have refrained from classifying them as suspicious nodules to avoid false-positive results. Expertise of radiologists is important to decrease false-positive screen results.[25]

New solid nodules are detected at each screening round in 5–7% of participants who undergo screening for lung cancer by low-dose CT, and have a higher probability of lung cancer than do baseline nodules. This factor should be considered in future screening guidelines. New solid nodules should be followed up more aggressively than nodules detected at baseline screening, for example by using lower volume cutoff values (<27 mm^3, 27 mm^3 to <206 mm^3, ≥206 mm^3). However, meticulous screening and follow-up with volume doubling time enables detection of new solid nodule lung cancer at an early stage. Nodule volume should be used to stratify the probability of lung cancer of new solid nodules, but more research into new nodules is necessary to identify how to optimise management of these nodules in lung cancer screening.

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Supplementary Appendix

Occurrence and lung cancer probability of new solid nodules at incidence CT lung cancer screening in the randomized NELSON trial

NELSON nodule management protocol

At first nodule detection, a nodule is classified by size:

NODCAT 1:
Nodules with benign characteristics (e.g. benign calcifications, fat component)
NODCAT 2:
Solid nodules <50mm³
Solid pleural based nodules <5mm in minimal diameter
Part-solid nodules <8mm in mean diameter
Part-solid nodules, solid component <50mm³
Non-solid nodules <8mm in mean diameter
NODCAT 3:
Solid nodules 50-500mm³
Solid pleural based nodules 5-10mm in minimal diameter
Part-solid nodules ≥8mm in mean diameter, and solid component <500 mm^3
Part-solid nodules, solid component 50-500mm³
Non-solid nodules ≥8mm in mean diameter
NODCAT 4:
Solid nodules >500mm³
Solid, pleural based nodules >10mm in minimal diameter
Part-solid nodules, solid component >500mm³

If a nodule is detected again at a subsequent screen, it is classified according to its growth rate. For nodules with a percentage volume change of >25%, volume-doubling time (VDT) is calculated. Nodules are then classified by growth rate:
GROWCAT A
Percentage volume change <25%
VDT >600 days
GROWCAT B
VDT 400-600 days
GROWCAT C
VDT <400 days

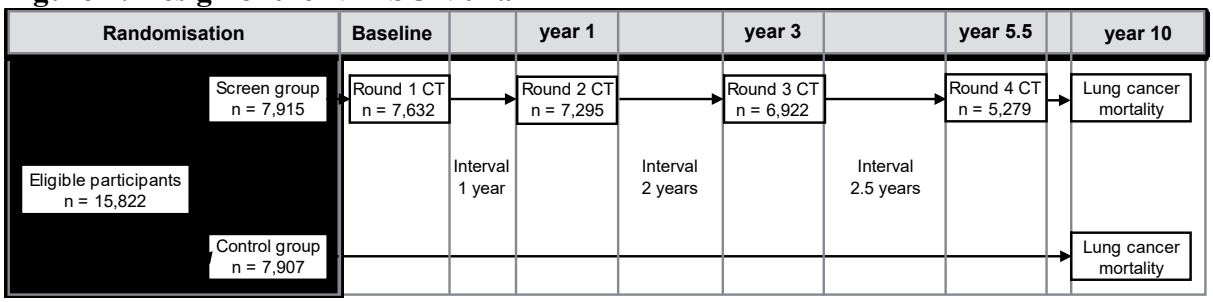
The screen result could be negative (invitation for the next screen round), indeterminate (invitation for a short-term follow-up CT to determine the VDT), or positive (referral for diagnostic work-up).

Referral algorithm for baseline nodules and pre-existing nodules in later screening rounds:
NEGATIVE:
NODCAT 1
NODCAT 2
INDETERMINATE, LEADING TO A NEGATIVE SCREEN AFTER FOLLOW-UP:

NODCAT 3 with GROWCATs A or B at follow-up examination
INDETERMINATE, LEADING TO A POSITIVE SCREEN AFTER FOLLOW-UP
NODCAT 3 with GROWCAT C at follow-up examination
POSITIVE:
NODCAT 4

Referral algorithm for new nodules at time of first detection in round 2 and 3:
NEGATIVE:
NODCAT 1
INDETERMINATE, LEADING TO A NEGATIVE SCREEN AFTER FOLLOW-UP:
NODCAT 2 with GROWCATs A or B at follow-up examination
NODCAT 3 with GROWCATs A or B at follow-up examination
INDETERMINATE, LEADING TO A POSITIVE SCREEN AFTER FOLLOW-UP
NODCAT 2 with GROWCAT C at follow-up examination
NODCAT 3 with GROWCAT C at follow-up examination
POSITIVE:
NODCAT 4

Figure 1: Design of the NELSON trial



Analyses of this study include data from the second screening round (annual screen) and the third screening round (biannual screen).

Calculations on participant-level

Receiver operating characteristic analysis was conducted for largest new nodule volume in a participant at first new nodule detection with eventual lung cancer diagnosis as outcome. Cut-off values were derived using a predefined overall sensitivity of 95% and Youden indexes as reference points for further adaption, optimizing intermediate and high-risk group. ROC analysis showed an area under the curve for nodule volume of 0.782 (95% confidence interval [95% CI]: 0.717, 0.842, P<0.0001). A cut-off value of ≥30mm^3 (sensitivity, 95.7% [95% CI: 85.0, 99.6]; specificity, 40.8% [95% CI: 37.2, 44.6]) for the largest new nodule provided >95% sensitivity. Participants with the largest new nodules <30mm^3 had a low lung cancer probability of 0.7% (2/281), whereas participants with the largest new nodule 30mm^3-<206mm^3 had an intermediate probability of 5.5% (17/308), and participants with the largest new nodule ≥206mm^3 had a high probability of 19.9% (28/141) (Table 2).

Table 1: Volume of largest new solid nodule and lung cancer risk (n=730; 683 participants without and 47 with eventual lung cancer diagnosis)*

* For 55 participants without and two with eventual lung cancer diagnosis exact volume measurement was not available and they were not considered in the calculations.

	Second and third screening round (participants with lung cancer/ all participants)	Lung cancer probability based on the largest nodule (95% CI)
All participants with new nodules	47/730	6.4% (3.2-5.6)
Volume of largest new nodule		
<25mm^3	1/241	0.4% (0.0-2.6)
25-<50mm^3	7/146	4.8% (2.2-9.7)
50-<100mm^3	6/109	5.5% (2.3-11.7)
100-<200mm^3	5/88	5.7% (2.1-12.9)
200-<300mm^3	6/36	16.7% (7.5-32.3)
300-<400mm^3	2/26	7.7% (1.0-25.3)
400-<500mm^3	3/20	15.0% (4.4-36.9)
≥500mm^3	17/64	26.6% (17.2-38.6)
Cut-off values		
<30mm^3	2/281	0.7% (0.0-2.7)
30-<206mm^3	17/308	5.5% (3.4-8.7)
≥206mm^3	28/141	19.9% (14.1-27.3)

Abbreviations: 95% CI - 95% confidence interval.

Table 2: Simulated diameter at first detection and lung cancer probability of new solid nodules (n=1,117; 1,069 benign nodules and 48 lung cancers)*

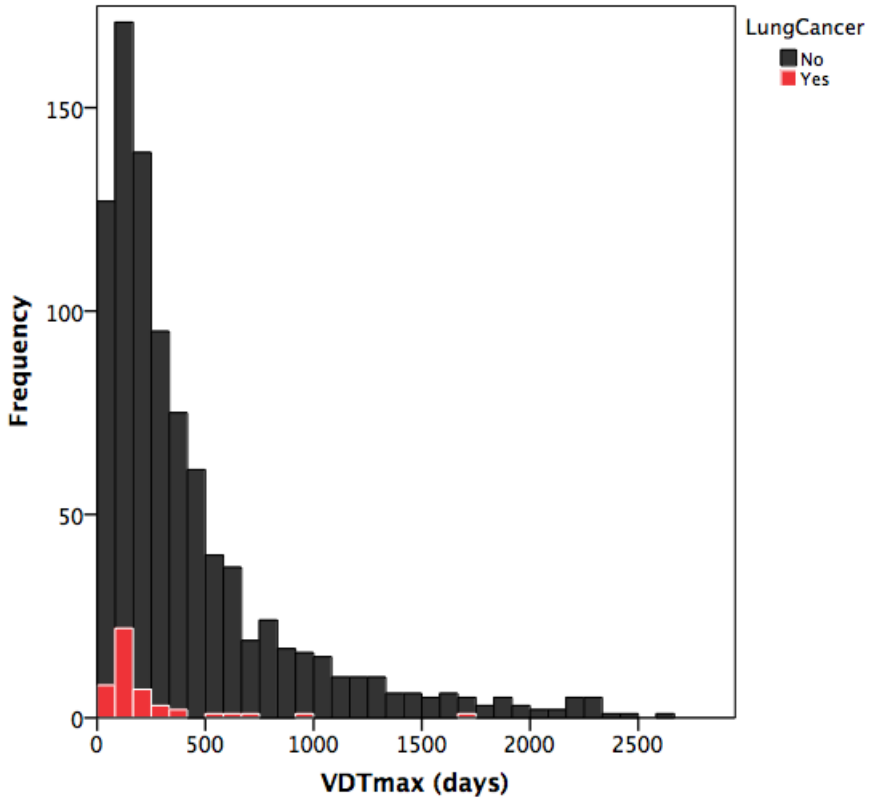
* For 103 benign nodules and two cancers no simulated diameter measurement was available and they were not considered in the calculations.

	Second screening round (lung cancer/total nodules)	Third screening round (lung cancer/total nodules)	Second and third screening round (lung cancer/total nodules)	Lung cancer probability (95% CI)
All Nodules	13/451	35/666	48/1117	4.3% (3.2-5.7)
Simulated mean diameter[a]				
<4mm	1/186	3/248	4/434	0.9% (0.3-2.4)
4-<6mm	5/135	5/194	10/329	3.0% (1.6-5.6)
6-<8mm	2/51	3/89	5/140	3.6% (1.3-8.3)
≥8mm	5/79	24/135	29/214	13.6% (9.6-18.8)
Cut-off values				
<3.7mm	1/155	1/199	2/354	0.6% (0.0-2.2)
3.7-<8.2mm	7/218	10/341	17/559	3.0% (1.9-4.9)
≥8.2mm	5/78	24/126	29/204	14.2% (10.0-19.7)

Abbreviations: 95% CI - 95% confidence interval.

[a] Diameters were simulated from computer generated volume measurements, based on three-dimensional voxels. Manually measured diameters are less accurate and will overestimate nodule size, which corresponds with lower lung cancer probabilities than presented in this table.

Figure 2: Estimated maximum volume doubling time (VDT_{max}) for benign and malignant new solid nodules



Risk prediction model

A risk prediction model was developed to assess whether the established relationship between the volume of the newly developed nodule and the occurrence of lung cancer diagnosis remained significant independent of other risk factors. The analyses were performed using R-version 3.2.3 and the R packages RMS, DCA, epiR and pROC.[1-5] The following risk factors were considered in the analysis: Age, gender, pack-years, smoking status, time in days since the previous scan, solid nodule count at baseline, nodule margin, nodule location, and nodule volume.

First, the univariate effect of the risk factors was assessed, as well as the effect of applying (non-) linear transformations of these factors. Backwards stepwise selection was used for variable selection, using a 5% significance level as a stopping criterion (based on Likelihood Ratio tests).

Table 3 shows the risk prediction model resulting from the backward stepwise selection. This model had an area under the receiver operating characteristic curve (AUC) of 0.825 (95% CI: 0.768, 0.882). The univariate effect of solely using the volume of the newly developed nodule

yielded an AUC of 0.795 (95% CI: 0.728, 0.862), with the difference between the two AUC's being non-significant (P=0.15). Thus, while considering additional risk factors improved the AUC-statistic, nodule volume was shown to be the most important risk factors for malignancy in a new nodule.

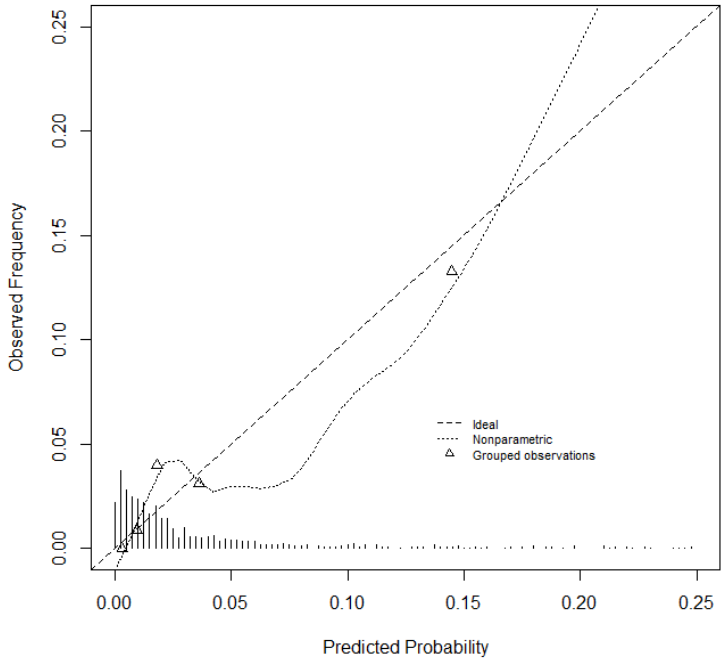
The calibration of the prediction model presented in Table 3 was investigated. A calibration plot was constructed, shown in Figure 3, which compares the estimated risks to the observed risks.[6] The 45-degree line, which can be described by an intercept of 0 and a slope of 1, describes perfect predictions. The calibration-in-the-large compares the overall estimated risk by the model to the observed risk in the dataset, which can be quantified as the intercept of the calibration plot.[7] The calibration-in-the-large provides an overview of whether the model over- or under-estimates risk and should be equal to 0. The model has a calibration-in-the-large of 0.0002 suggesting a good overall mean calibration. The calibration slope represents the agreement with the 45-degree line in the calibration plot and represents the amount of overfitting. The calibration slope should be equal to 1. The calibration slope of the model was 1.0001, which suggests no overfitting. Overall, these analyses suggest the model has good internal calibration.

Decision curve analysis was performed to assess the range of risk thresholds for which there is a net benefit of using the risk prediction model. The decision curve analysis in Figure 4 shows that there is a net benefit for using the model compared with assuming none of the nodules are cancerous and assuming all of the nodules are cancerous across probability thresholds of 0% to at least 14%. The specificity of the model was assessed at the lowest and highest risk thresholds that give a similar sensitivity as a cut-off value of $\geq 27 mm^3$ based on volume alone (sensitivity, 95.8% [95% CI: 85.2, 99.6]; specificity, 38.3% [95% CI: 35.5, 41.3]). The corresponding cut-offs for the risk model are 1.2 %, which yields a sensitivity of 95.8% (95% CI: 85.8, 99.5%) and a specificity of 38.3% (95% CI: 35.4, 41.2) and 1.68% (sensitivity, 95.8% [95% CI: 85.8, 99.5]; specificity, 48.8% [95% CI: 45.8, 53.8]), suggesting that considering additional risk factors may improve specificity somewhat. However, nodule volume has been shown to be the most significant risk factor for lung cancer in new solid nodules.

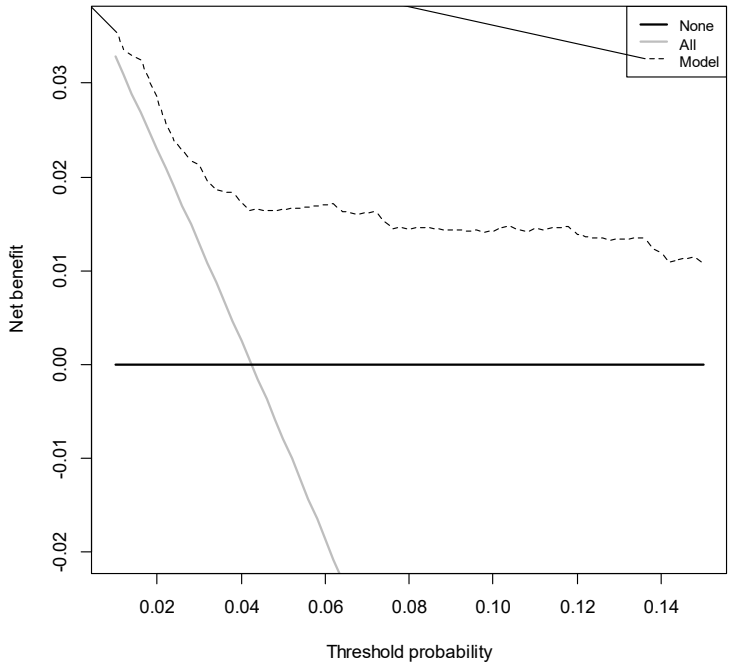
Table 3: Risk prediction model resulting from backward stepwise selection

Parameter	Coefficient	Standard error	P-value
Model constant	-10.8698	1.9213	-
One solid nodules at the baseline scan (compared to none)	-1.4106	0.6475	0.0294
Two solid nodules at the baseline scan (compared to none)	-1.1416	1.0562	0.2798
Three solid nodules at the baseline scan (compared to none)	-1.4110	1.0437	0.1764
Four solid nodules at the baseline scan (compared to none)	-1.5970	1.1109	0.1506
Five solid nodules at the baseline scan (compared to none)	-7.8827	31.3761	0.8016
Six or more solid nodules at the baseline scan (compared to none)	-0.4598	1.0557	0.6631
Nodule location in upper lobe (compared to lower lobe)	0.6724	0.3259	0.0391
Logarithmic transformation of number of days since the previous scan	0.5637	0.2796	0.0438
Logarithmic transformation of the new nodule volume (in mm^3)	0.9011	0.1150	<0.0001

Supplementary Figure 3: Calibration plot of the prediction model



Supplementary Figure 4: Decision curve analysis of the prediction model



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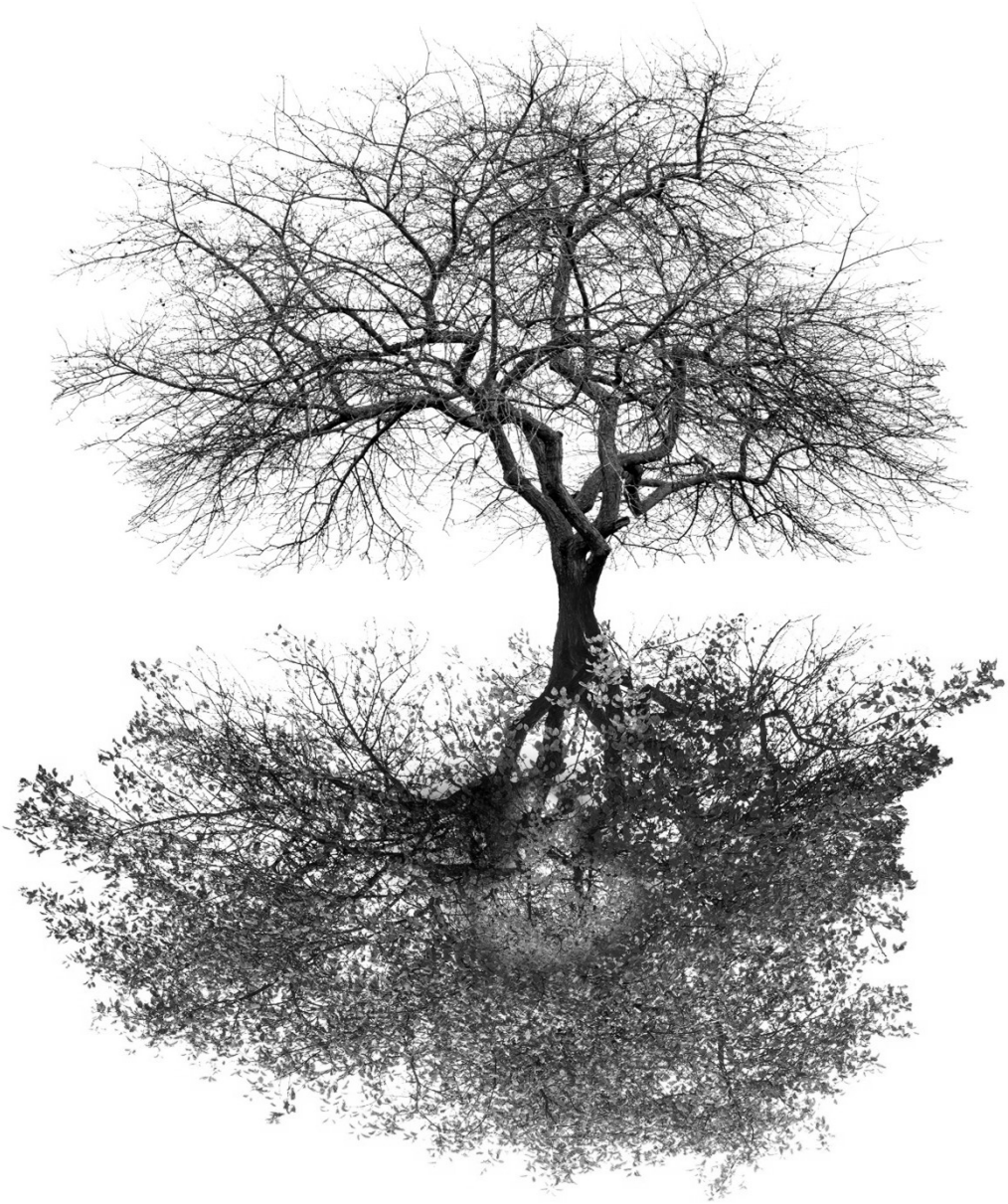

Chapter 5

Persisting new nodules in incidence rounds of the NELSON CT lung cancer screening study

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ABSTRACT

Background: US guidelines recommend low-dose CT (LDCT) lung cancer screening for high-risk individuals. New solid nodules after baseline screening are common and have a high lung cancer probability. Currently, no evidence exists concerning the risk stratification of nonresolving new solid nodules at first LDCT screening after initial detection.

Methods: In the Dutch-Belgian Randomized Lung Cancer Screening (NELSON; trialregister.nl, ISRCTN63545820) Trial, 7,295 participants underwent the second and 6,922 participants the third screening round. We included participants with solid nodules, that were registered as new or <15mm³ (study detection limit) at previous screens and received additional screening after initial detection; thereby excluding high-risk nodules according to the NELSON management protocol (nodules ≥500mm3).

Results: Overall, 680 participants with 1,020 low- and intermediate-risk new solid nodules were included. A total of 562 (55%) new solid nodules were resolving, leaving 356 (52%) participants with a nonresolving new solid nodule of whom 25 (7%) were diagnosed with lung cancer. At first screening after initial detection, volume doubling time (VDT), volume, and VDT combined with a predefined ≥200mm3 volume cutoff had high discrimination for lung cancer (VDT, area under the curve [AUC]: 0.913; volume, AUC: 0.875; VDT and ≥200mm3 combination, AUC: 0.939). Classifying a new solid nodule with either ≤590days VDT or ≥200mm3 volume positive provided 100% sensitivity, 84% specificity, and 27% positive predictive value for lung cancer.

Conclusions: More than half of new low- and intermediate-risk solid nodules in LDCT lung cancer screening resolve. At follow-up, growth assessment potentially combined with a volume limit can be used for risk stratification.

Introduction

Lung cancer remains a leading cause of cancer-related death worldwide and numerous trials are exploring lung cancer screening by low-dose computed tomography (LDCT) to improve prognosis.[1,2] The National Lung Screening Trial showed a 20% reduced lung cancer mortality when comparing LDCT to chest radiography.[3] Accordingly, most US guidelines currently recommend LDCT lung cancer screening for high-risk individuals,[4–6] while European stakeholders are awaiting the final results of the Dutch–Belgian lung cancer screening (NELSON) trial.[5,7]

Previously, research focused on nodules detected at baseline screening, but with increasing duration of a trial its success depends on the management of new nodules.[7–9] While baseline nodules might have been present for years before detection, new nodules found after baseline by definition have developed within a short timeframe. However, there is only limited evidence for the management of new nodules and published data uses different definitions of incident nodules.[4,8,10–12] Available data of the Early Lung Cancer Action Project (ELCAP),[13] the International-ELCAP (I-ELCAP),[14] the Pittsburgh Lung Screening Study (PLuSS),[15] the Mayo trial,[16] NLST[17] and the NELSON trial[8] suggest that anually between 3-13% of participants develop a new nodule after baseline screening. Recently, the NELSON trial provided a first in-depth analysis of new solid nodules and proposed lower cutoff values for new nodules as compared to baseline nodules,[8] which were adopted in a European position statement on lung cancer screening.[7] Nodule risk stratification is based on a nodule's lung cancer probability, with only high-risk nodules (commonly >15% lung cancer probability) warranting immediate referral of a participant to a specialist, whereas low (commonly <1% lung cancer probability) and intermediate risk nodules receive additional screening LDCT scans.[7,8,11,18,19] While size-based management strategies for initial new nodule detection have been proposed, with nodules ≥200mm^3 being high-risk,[7,8,20] there is insufficient evidence concerning the management of low and intermediate risk new nodules at subsequent screening. Furthermore, pulmonary nodules are known to be dynamic,[21,22] but few studies have assessed resolving nodules in general and mostly focussed on subsolid nodules.[22–25]

The aim of this study was to investigate the final outcome of new solid nodule nature at first follow-up or regular screening after initial new solid nodule detection in incidence screening rounds of LDCT lung cancer screening.

Methods

Participants

Recruitment process and study design of the NELSON trial (trialregister.nl, number ISRCTN63545820) have been published before.[26–28] Summarized, eligible patients were adults aged 50–75 years, who had smoked >15 cigarettes per day for >25 years or >10 cigarettes per day for >30 years and were still smoking or stopped smoking <10 years previously. The NELSON trial was approved by ethics boards of all participating centers. All participants provided written informed consent. Between December 2003 and July 2006, 15,792 participants from four centers in the Netherlands and Belgium were randomized to low-dose chest CT screening (n=7,900) or no screening (n=7,892) and between April 2004 and December 2006, 7,557 participants underwent baseline screening. Within the NELSON trial's protocol, participants were followed up for 10 years after randomization.[27] For this analysis, participants with a solid non-calcified nodule initially detected in the second (annual screening) or third (biannual screening) screening round and registered by the NELSON radiologists as new or <15mm^3 (study detection limit) at previous screens were included if they had one additional screening LDCT within the NELSON trial. New nodules initially detected in the fourth round (2.5 year screening interval), which only included a subgroup of patients with a higher proportion of current smokers and more participants with at least one non-negative screening,[29] were not included to avoid confounding through this selection. Participants referred immediately for diagnostic work-up after initial new nodule detection and participants without any further screening LDCT were excluded from this analysis.

Procedures and Nodule management

The CT scan procedures were published before and are described in the Supplementary Appendix.[26,28] New solid nodules were classified into four categories (NODCAT I-IV): Calcified nodules or nodules with other benign characteristics (NODCAT I, regular screening), new solid nodules 15-50mm^3 (NODCAT II, follow-up

LDCT within 1 year), new solid nodules 50-500mm^3 (NODCAT III, follow up LDCT within 6-8 weeks), and new solid nodules ≥500mm^3 (NODCAT IV, immediate referral to pulmonologist).[26] After initial detection, a nodule's subsequent evaluation was based on volume doubling time (VDT, Supplementary Appendix). A smaller VDT signifies faster nodule growth.

For this study, the original nodule data as reported by the NELSON radiologists were used. A nodule detected after baseline was considered new if registered by the radiologists as new or below the study detection limit of 15mm^3 on the previous scan. A new nodule was considered resolving if the NELSON radiologists did not register it on the subsequent LDCT after detection due to disappearance or if only a non-measurable scar or calcified nodule persisted.

Malignancy and benignity was determined on the basis of histology and diagnostic work-up according to national and international guidelines and, in case of benignity, also on a negative final screening result in the NELSON trial and no interval or post-screening lung cancer according to the national cancer registries of the Netherlands and Belgium and medical file review.[9,19,26]

Statistical Analysis

Non-normally distributed continuous variables were analyzed using the Mann-Whitney U test and described as medians and interquartile ranges (IQR). Fisher's exact test was used to analyze nominal variables. The 95% confidence intervals (CI) were calculated with the Agresti-Coull method.

The VDT was calculated for all nonresolving new solid nodules based on the volume at initial detection and first screening after initial detection. For nodules that decreased in size, the consequently negative VDT was converted to positive by subtracting it from the maximum (thus slowest) observed positive VDT to enable receiver operating characteristic (ROC) analysis with all nodules. The European position statement on lung cancer adopted a ≥200mm^3 cutoff for high-risk new solid nodules from the NELSON trial's results.[7,8] This cutoff was combined with VDT using a binary logistic regression model. Receiver operating characteristic (ROC) analysis was performed for VDT and volume at follow-up, as well as for the model probabilities of the combination of VDT and ≥200mm^3, with eventual lung cancer diagnosis as outcome. ROC curve comparison was performed using the method described by DeLong et al.[30]

Optimized cutoffs for VDT and volume were derived using Youden Indices as reference points for further adaption.[31] The identified VDT cutoff was also assessed with the predefined ≥200mm^3 volume cutoff, classifying a nodule positive when at least one criterion was fulfilled. Additionally, predefined VDT cutoffs of <400 days, 400-600 days and VDT >600 days were assessed. Missing data were excluded from the respective analyses and are referenced below the respective Tables and Figures.
Corresponding calculations for simulated mean diameter (mean of longest and perpendicular simulated diameter) as well as cutoff analyses on participant level based on the largest or fastest-growing nodule are presented in the Appendix.
All statistical tests were two-sided. Statistical analyses were performed with SPSS version 25.0 (IBM) and R (version 3.3.3).

Results

Overall, 680 participants with 1,020 new solid nodules and a follow-up or regular screening LDCT were included (Figure S1). Median age of included participants was 59 years (IQR 55-63) at baseline, 76% (514/680) were male, and median smoking pack-years at baseline were 39 (IQR 30-49) (Table S1). Of the 1,020 included nodules, 25 (2.5%) were lung cancer and 232 (23%) could be identified in retrospect as minuscule opacity smaller than the detection limit (15mm^3).

Resolving and nonresolving new solid nodules

A total of 562 (55%) of the 1,020 new solid nodules were resolving. In 321 (47%) participants all detected new solid nodules resolved, leaving 458 (45%) nonresolving new nodules and respectively 359 (53%) participants with at least one nonresolving new nodule. New solid nodules visible in retrospect as minuscule opacity below the trial's detection limit were less likely to resolve compared to those not visible in retrospect (22% [50/232] vs. 65% [512/788], P<0.0001), and tended to be smaller at initial detection with a median of 18mm^3 (IQR 16-21mm^3) versus 52mm^3 (IQR 29-121mm^3, P<0.0001). In total, 97% [224/232] of the nodules visible in retrospect as minuscule opacity were <50mm^3 at initial detection and the lung cancer probability (1.3% [3/224], CI 0.3-4.0%) was similar compared to new solid nodules <50mm^3 and not visible in retrospect (1.5% [6/394], CI 0.6-3.4%, P=0.855, Table S2).

Nonresolving new solid nodules

In 4 (1.1%) of the 359 participants with nonresolving new solid nodules a benign new solid nodule changed to part-solid (n=3) or pure ground-glass (n=1) and in 3 (0.8%) participants these nodules were the only new nodules detected. Excluding the 3 participants with only subsolid nonresolving new nodules, characteristics of the 356 participants with at least one new solid nodule that persisted are presented in Table S3.

In 25 (7.0%) of the 356 participants a nonresolving new solid nodule was lung cancer corresponding to 25 (5.5%) of the 454 nonresolving new solid nodules. At time of diagnosis, 23 (92%) of the lung cancers were stage I with adenocarcinoma (16/25 [64%]) being the most common histology (Table S4). At first follow-up or regular screening LDCT, VDT, volume, and simulated mean diameter differed significantly between benign nodules and lung cancers (Table 1). ROC analysis demonstrated an area under the curve (AUC) of 0.913 (95%CI 0.861-0.965) for VDT, 0.875 (95%CI 0.822-0.928) for nodule volume, and 0.939 (95%CI 0.904-0.974) for VDT combined with the predefined ≥200mm^3 cutoff (Figure 1). The AUC of VDT and ≥200mm^3 was superior to volume (P=0.0322) and statistically comparable to VDT alone (P=0.0535). Lung cancer probabilities of nodules stratified by the identified cutoff values for VDT (≤590 days) and nodule volume (≥65mm^3), as well as the optimized VDT cutoff of ≤590 days together with the predefined ≥200mm^3 volume cutoff are shown in Table 2. The performance of these cutoff values stratified by time until first LDCT after initial detection is displayed in Table 3. Table S5 summarizes the performance of the predefined VDT cutoffs of <400 days, 400-600 days and VDT >600 days for comparison. In total, 8.3% (1/12) of new solid nodules with a VDT of 400-600 days and 34% (22/64) of nodules with VDT <400 days were lung cancer. The respective results stratified by the visibility of the new solid nodule in retrospect is presented in Table S6. Using the ≤590 days VDT cutoff together with the predefined ≥200mm^3 volume cutoff reached 100% (95%CI 84-100%) sensitivity, 84% (95%CI 80-87%) specificity, 27% (95%CI 19-37%) positive predictive value, and 100% (95%CI 99-100%) negative predictive value for discriminating lung cancer. The respective analyses based simulated mean diameter and calculations based on participant level can be found in Tables S7-S9 and Figures S2 and S3. The discriminative performance (AUC) of volume compared to simulated-mean diameter was superior (P=0.0011) (Figure S1).

	All new solid nodules that persisted on the first LDCT after detection, n=454 (100%)			Subsequent LDCT within 120 days, n=210 (46%) (short-term follow-up)			Subsequent LDCT after 120 days, n=244 (53%)		
	Benign, 429/454 (94.5%)	Lung cancer, 25/454 (5.5%)	P-Value	Benign, 193/210 (91.9%)	Lung cancer, 17/210 (8.1%)	P-Value	Benign, 236/244 (96.7%)	Lung cancer, 8/244 (3.3%)	P-Value
Days between scans									
Median (IQR)	347 (50-724)	56 (46-325)	0.006	49 (43-62)	49 (42-56)	0.887	719 (370-797)	347 (323-640)	0.011
Volume (mm^3)									
<50mm^3	296/429 (69.0%)	1/25 (4.0%)		85/193 (44.0%)	1/17 (5.9%)		216/236(89.4%)	0/8 (0.0%)	
50-<500mm^3	120/429 (28.0%)	22/25 (88.0%)		95/193 (49.2%)	14/17 (82.4%)		25/236 (10.6%)	8/8 (100%)	
≥500mm^3	13/429 (3.0%)	2/25 (8.0%)		13/193 (6.7%)	2/17 (11.8%)		0/236 (0.0%)	0/8 (0.0%)	
Median (IQR)	28 (17-63)	135 (83-331)	<0.0001	63 (33-126)	203 (95-362)	0.0003	20 (15-30)	94 (79-248)	<0.0001
VDT (days)									
Median (IQR)	∞ (1845-∞)	219 (129-298)	<0.0001	∞ (1346-∞)	155 (116-294)	<0.0001	∞ (1969-∞)	254 (227-362)	<0.0001
Simulated mean diameter* ***(mm)***									
Median (IQR)	4.0 (3.2-5.8)	7.2 (5.5-9.1)	<0.0001	5.6 (4.0-7.4)	8.0 (5.4-10.9)	0.014	3.5 (3.0-4.1)	7.0 (5.5-8.5)	<0.0001
Nodule was below detection limit in retrospect	176/429 (41.0%)	4/25 (16.0%)	0.012	17/193 (8.8%)	1/17 (5.9%)	0.999	159/236 (67.4%)	3/8 (37.5%)	0.127

Table 1: Characteristics of nonresolving new solid nodules that persisted as solid nodule on the first follow-up or regular screening after initial detection

N=454; 429 benign nodules and 25 lung cancer nodules

Abbreviations: ∞ - decreased size, IQR - Interquartile range, LDCT – Low-dose computed tomography, VDT - Volume doubling time.

**Diameters were simulated from computer-generated volume measurements, based on three-dimensional voxels. Manually measured diameters are less accurate and will overestimate nodule size.*

	All new solid nodules that persisted on the first LDCT after detection		Subsequent LDCT within 120 days (short-term follow-up)		Subsequent LDCT after 120 days	
	Lung cancer/all nodules meeting criterion	Lung cancer probability (95% CI)	Lung cancer/ all nodules meeting criterion	Lung cancer probability (95% CI)	Lung cancer/ all nodules meeting criterion	Lung cancer probability (95% CI)
VDT						
>590 days	2/362	0.6% (0.0-2.1)	2/139	1.4% (0.1-5.4)	0/223	0.0% (0.0-2.0)
≤590 days	23/75	30.7% (21.3-41.9)	15/56	26.8% (16.9-39.7)	8/19	42.1% (23.1-63.8)
Volume						
<65mm^3	1/314	0.3% (0.0-2.0)	1/95	1.1% (0.0-6.3)	0/219	0.0% (0.0-2.1)
≥65mm^3	24/123	19.5% (13.4-27.5)	16/100	16.0% (10.0-24.5)	8/23	34.8% (18.7-55.2)
VDT and volume						
>590 days and <200mm^3	0/345	0.0% (0.0-1.3)	0/124	0.0% (0.0-3.6)	0/221	0.0% (0.0-2.1)
≤590 days or ≥200mm^3	25/92	27.2% (19.1-37.1)	17/71	24.6% (15.9-36.0)	8/21	38.1% (20.7-59.2)

Table 2: Lung cancer probability of nonresolving new solid nodules stratified by volume doubling time and volume at first follow-up or regular screening after initial detection

N=437; 412 benign nodules and 25 lung cancer nodules

Abbreviations: CI - Confidence interval, IQR - Interquartile range, LDCT – Low-dose computed tomography, VDT - Volume doubling time.

Exact volume measurement was not available or classification based on radiologist's size categorization was unattainable for 17 benign nodules, and they were not included in the calculations.

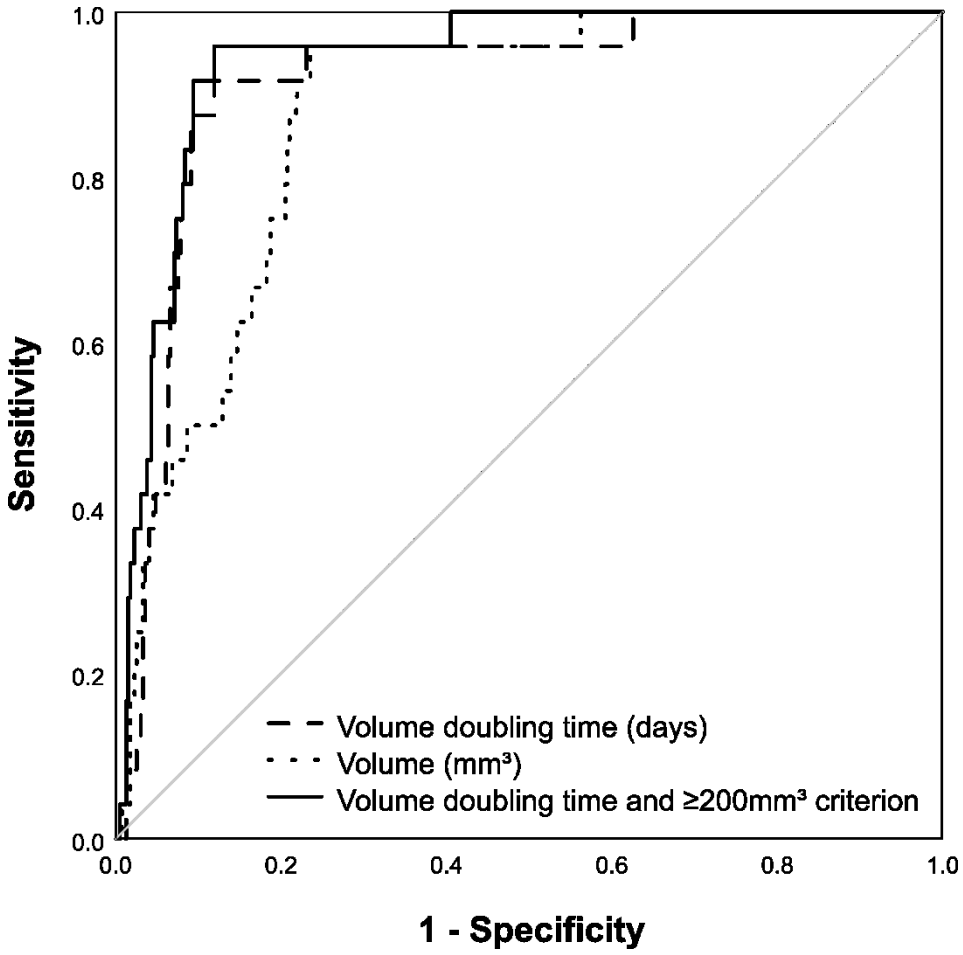

Figure 1: Receiver operating characteristic curves* of volume doubling time, nodule volume and the combination of volume doubling time and ≥200mm³ at first follow-up or regular screening after initial detection for discrimination of lung cancer.

Volume doubling time (AUC: 0.913, 95%CI 0.861-0.965, P<0.0001); Volume (AUC: 0.875, 95%CI 0.822-0.928, P<0.0001); Volume doubling time and ≥200mm³ criterion (AUC: 0.939, 95%CI 0.904-0.974, P<0.0001). AUC=area under the curve.

* Exact volume measurement was not available for 34 benign nodules and one lung cancer, and they were not included in the calculations.

	All new solid nodules that persisted on the first LDCT after detection	Subsequent LDCT within 120 days (short-term follow-up)	Subsequent LDCT after 120 days
VDT ≤590 days			
Sensitivity (95% CI)	23/25, 92.0% (73.9-98.9)	15/17, 88.2% (64.4-98.0)	8/8, 100% (62.8-100)
Specificity (95% CI)	360/412, 87.4% (83.8-90.3)	137/178, 77.0% (70.2-82.6)	223/234, 95.3% (91.7-97.4)
PPV (95% CI)	23/75, 30.7% (21.3-41.9)	15/56, 26.8% (17.5-41.0)	8/19, 42.1% (23.1-63.8)
NPV (95% CI)	360/362, 99.4% (97.9-100)	137/139, 98.6% (94.6-99.9)	223/223, 100% (98.0-100)
VDT ≤590days or volume ≥200mm^3			
Sensitivity (95% CI)	25/25, 100.0% (84.2-100)	17/17, 100.0% (78.4-100)	8/8, 100% (62.8-100)
Specificity (95% CI)	345/412, 83.7% (79.9-87.0)	124/178, 69.7% (62.5-76.0)	221/234, 94.4% (90.6-96.8)
PPV (95% CI)	25/92, 27.2% (19.1-37.1)	17/71, 24.6% (15.9-36.0)	8/21, 38.1% (20.7-59.2)
NPV (95% CI)	345/345, 100.0% (98.7-100)	124/124, 100.0% (96.4-100)	221/221, 100.0% (97.9-100)
Volume ≥65mm^3			
Sensitivity (95% CI)	24/25, 96.0% (78.9-100)	16/17, 94.1% (71.1-100)	8/8, 100% (62.8-100)
Specificity (95% CI)	313/412, 76.0% (71.6-79.9)	94/178, 52.8% (45.5-60.0)	219/234, 93.6% (89.6-96.2)
PPV (95% CI)	24/123, 19.5% (13.4-27.5)	16/100, 16.0% (10.0-24.5)	8/23, 34.8% (18.7-55.2)
NPV (95% CI)	313/314, 99.7% (98.0-100)	94/95, 98.9% (93.7-100)	219/219, 100% (97.9-100)

Table 3: Performance of the identified cutoffs at first follow-up or regular screening after initial detection

(N=437; 412 benign nodules and 25 lung cancer nodules)

Abbreviations: IQR - Interquartile range, LDCT – Low-dose computed tomography, NPV - Negative predictive value, PPV - Positive predictive value, VDT - Volume doubling time.

Exact volume measurement was not available or classification based on radiologist's size categorization was unattainable for 17 benign nodules, and they were not included in the calculations.

Discussion

This study focused on new solid nodules detected in incidence screening rounds (annual and biannual screening) of the NELSON trial and at least one additional screening LDCT. These nodules are low and intermediate risk according to the NELSON management protocol, since participants with high-risk nodules were referred immediately to a pulmonologist without additional follow-up.[26]

We report three major findings. First, 55% of the new solid nodules included were resolving (65% of the nodules not visible in retrospect, 22% of those visible in retrospect as a minuscule opacity below detection limit), and in 47% of the included participants all detected new solid nodules were resolving. Second, eventually, 7.0% of the participants with a nonresolving new solid nodule that persisted as solid nodule had lung cancer in such a nodule, with 5.5% of the nonresolving new solid nodules that persisted as solid nodule being diagnosed as lung cancer. Third, at first screening LDCT after initial detection, VDT (AUC: 0.913) and volume (AUC: 0.875) had high discriminatory power. The combination of VDT and the previously established ≥200mm^3 high-risk cutoff (AUC: 0.939) outperformed volume alone but was not significantly better than VDT alone (P=0.0535). Employing the identified ≤590 days VDT cutoff together with the ≥200mm^3 high-risk cutoff, thereby classifying nodules positive when at least one criterion was fulfilled, provided 100% sensitivity and 84% specificity for discriminating lung cancer.

A previous study of the NELSON trial examined solid baseline nodules sized 50-500mm^3 and reported that 90% (867/964) of the nodules persisted, with 3% (27/867) of nonresolving nodules being diagnosed as lung cancer.[24] In this study, 44% of new solid nodules sized 50-500mm^3 at initial nodule detection persisted with 10% being lung cancer, underlining the high lung cancer risk of new nodules. In an earlier study, we observed that with longer screening interval the number of new nodules did not increase proportionally while the percentage of lung cancers rose.[8] This phenomenon could be explained by the nature of nonresolving new nodules: The longer a screening interval, the higher the proportion of nonresolving new nodules and consequently the higher the percentage of lung cancers. Therefore, the screening interval length prior to detection might carry implications for the significance and potential lung cancer probability of a new nodule. Similarly, new nodules visible as a very small opacity in

retrospect were less likely to resolve than new nodules not visible at all. This corroborates the finding that at equivalent size, visibility as very small nodule in retrospect is significantly associated with lung cancer when compared to new nodules not visible at all.[20]

In our previous study concerning risk-stratification of new solid nodules at initial detection, it was shown that new solid nodules <30mm^3 (adapted from 27mm^3; low risk, <1% lung cancer probability) should continue regular screening, new solid nodules between 30-<200mm^3 (intermediate risk, around 3% lung cancer probability) represent an indeterminate subgroup requiring short-term follow-up by LDCT, and new solid nodules ≥200mm^3 (around 17% lung cancer probability) should be referred for diagnostic evaluation.[7,8] This study investigated the management approach for low and intermediate risk new solid nodules at first LDCT after initial detection. Risk stratification by VDT and size (volume, simulated diameter) reached comparable sensitivities, but VDT displayed a superior specificity, especially at short-term follow-up. The observed statistically optimal VDT cutoff of ≤590 days is analogous to currently employed cutoffs of ≤600 days, such as in the British Thoracic Society guideline for the investigation and management of pulmonary nodules and the NELSON management protocol,[7,11,26] and its appropriateness is confirmed for the first time in new solid nodules. Based on previous findings of the NELSON trial, the British Thoracic Society guideline considers nodules with a VDT between 400-600 days as intermediate risk group and nodules with a VDT <400 days as high-risk group.[11,19,26] While the overall performance of the VDT risk-stratification approach has been confirmed for low- and intermediate-risk new solid nodules with 30% (23/76) of new solid nodules with a VDT ≤600 days being lung cancer (8.3% [1/12] of nodules with VDT 400-600 days and 34% [22/64] of nodules with VDT <400 days), further research is required to determine whether immediate referral might be appropriate for all low- and intermediate-risk new solid nodules with a VDT ≤600 days. Furthermore, any employed follow-up time interval should enable the detection of the target VDT cutoff. Given that lung cancer growth was shown to not always be exponential or linear,[32,33] addition of a volume limit compelling referral to a pulmonologist might prevent slow growing lung cancers from evading timely referral. While this approach further increased the sensitivity of the risk-stratification approach, it decreased its specificity and could potentially lead to overdiagnosis. Addition of a ≥200mm^3 volume limit to

VDT reclassified 17 persisting new nodules as positive with 11% (2/17) being lung cancer. Further research is necessary to confirm the utility of such a volume limit.
Results concerning newly detected nodules in lung cancer screening may also apply to incidentally detected nodules found in routine care.[8,34] The results and cutoffs should only be extrapolated in a population with similar epidemiology characteristics to the population investigated here. Importantly, the size of new nodules detected in a specified timeframe reflects its growth rate and incidentally detected new nodules in clinical practice could benefit from calculation of the maximal VDT (slowest possible VDT).[8]

This study has limitations. Nodules <15mm^3 were not registered in the NELSON trial. Additionally, with increasing trial length, radiologists potentially gained increased expertise in distinguishing scars or infections from suspicious lesions and might have refrained from classifying them as suspicious nodules to avoid false-positive results. Expertise of radiologists is important to decrease false-positive screen results.[35] The possibility that the actual number of very small new solid nodules is somewhat higher than reported here cannot be excluded. The screening intervals were predefined in the trial and do not directly translate to clinical practice, where new nodules might be found after even shorter or longer intervals. This was a secondary analysis of patients with new solid nodules and at least one screening after initial new nodule detection. While 1,020 low or intermediate-risk new nodules of 680 participants were assessed, the proportion of lung cancers was, as anticipated, moderate (25 lung cancers) and further multivariate analyses were not performed. An extensive analysis of new solid nodule characteristics has been conducted previously.[20] The analyses performed grouped new solid nodules that were visible as a minuscule opacity in retrospect together with new solid nodules not visible in retrospect. Nevertheless, the cutoff values performed adequately in both nodule groups. Within the NELSON management protocol, new nodules with a VDT ≤400 days were referred for further diagnostic work-up. To minimize bias through the protocol, this analysis incorporated all follow-up data within the NELSON trial including cancer diagnosis in later rounds and post-trial information from the national cancer registries.

This study completes our previously established size-based management approach at initial new solid nodule detection with volume cutoffs of <30mm³, 30mm³ to

<200mm³ and ≥200mm³ representing low-, intermediate- and high-risk groups respectively.[8] After initial detection, in about half of participants all detected low- and intermediate-risk new solid nodules resolve until the next LDCT examination. Eventually, in 7.0% of participants with nonresolving low- and intermediate-risk new solid nodules the final new nodule outcome is lung cancer and an aggressive management strategy is warranted. At first screening after initial detection, a new solid nodule with a VDT ≤600 days has a high lung cancer probability and potentially requires immediate referral to a pulmonologist. Addition of a ≥200mm^3 volume limit for new solid nodules that compels immediate referral as well, might further increase the sensitivity of the risk stratification by VDT.

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Supplementary Appendix

Final outcome of new nodule nature at incidence screening with low-dose CT: analysis of data from the randomized, controlled NELSON trial

Supplementary Methods

CT scan procedure

The four screening sites used 16-MDCT scanners or 64-MDCT scanners (Sensation-16, Siemens Medical Solutions, Forchheim, Germany; or Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Best, Netherlands). Datasets were derived from images of the thorax with 1.0mm slice width and a 0.7mm reconstruction interval. In the first two rounds, two independent radiologists evaluated each CT scan individually, and a third reader decided ultimately in case of discrepancy.[1,2] In the third and fourth screening round, single reading was performed. It was shown before that double reading consensus has no benefit with the use of semiautomated software.[3] CT data analysis was performed on digital workstations (Leonardo, Siemens Medical Solutions) using software for semiautomated volume measurements (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions). Based on the three-dimensional nodule volume, this software also simulated longest and perpendicular nodule diameter in the axial plane. Radiologists were allowed to overrule protocol-based screening result (done for 195 [6%] of 3,318 participants at the baseline screening round) and manually adjust the volume measurement in case of inappropriate segmentation.[4] Manual adjustments occurred in case of high suspicion of malignancy (eg, enlarged mediastinal lymph nodes) or benignity (eg, benign calcification patterns)[4]. Individual matching of nodules on subsequent LDCT scans was based on the software's matching algorithm (depending on consistency, size and location) and the radiologist's visual confirmation of the matching. Data generated during CT evaluation were uploaded to the NELSON management system.[1]

Volume Doubling Time

$$VDT(days) = \frac{[ln2 \times \Delta t]}{[ln\,(V2/V1)]}$$

in which Δt represents the time between scans in days, V1 represents the volume of the new solid nodule at initial new nodule detection, and V2 represents the volume of the new solid nodule at first-follow up scan.

Calculations on Participant-level

Based on the fastest growing nodule or largest nodule respectively, receiver operating characteristic analysis showed an area under the curve for the volume doubling time (VDT) of 0.901 (95% confidence interval [95% CI]: 0.846, 0.956, P<0.0001) and for nodule volume of 0.849 (95% confidence interval [95% CI]: 0.790, 0.908, P<0.0001). The identified cutoffs correspond to those found in the nodule-based analysis and the lung cancer probabilities as well as the cutoff performance are shown in Supplementary Table 3 and 4.

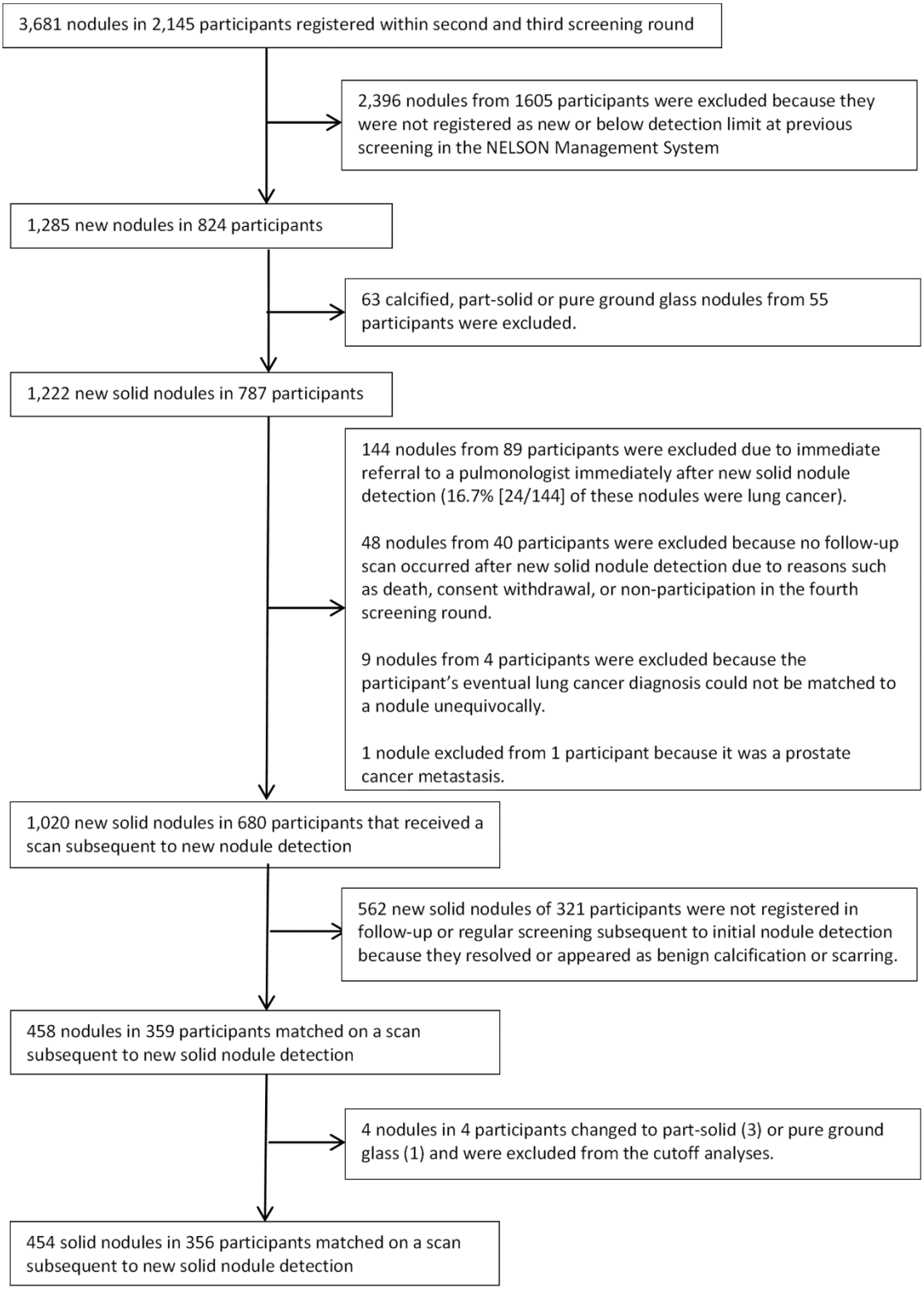

Figure S1: Flowchart of new solid nodules detected within second and third screening round
Some participants had a new nodule and, for example, a previously missed nodule. Whereas the missed nodule was excluded, the new nodule (and therefore the participant) was included.

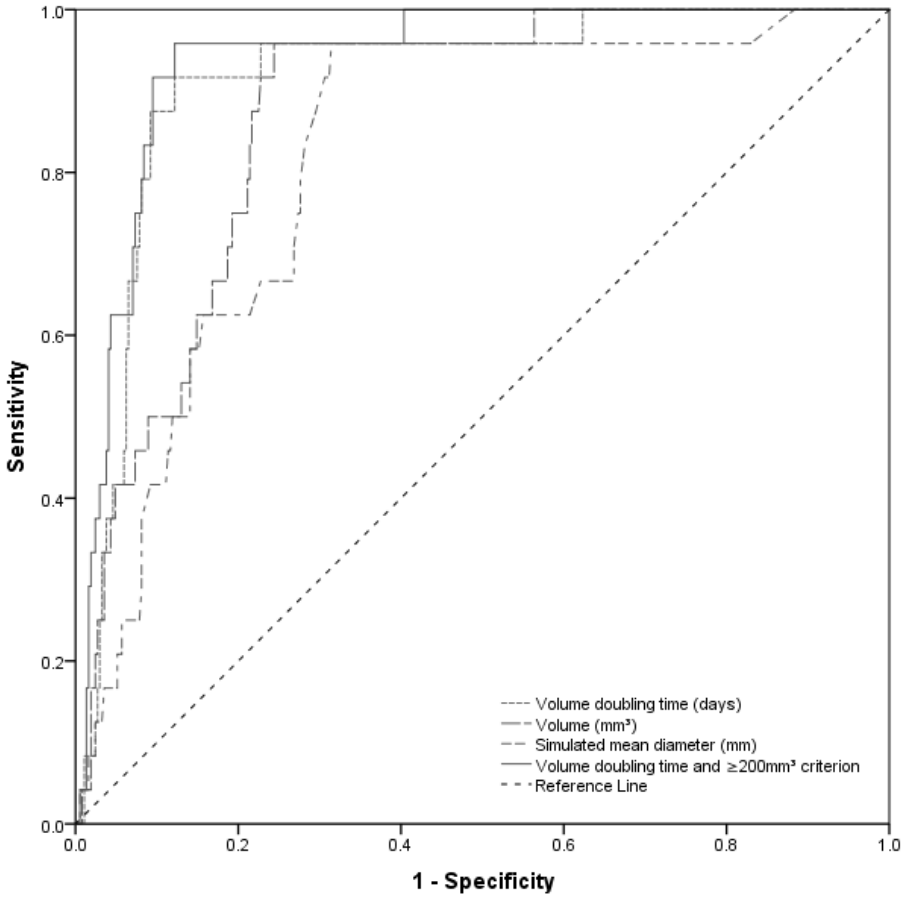

Figure S2: Receiver operating characteristic curves* of volume doubling time, nodule volume, simulated mean diameter and the combination of volume doubling time and ≥200mm^3 at first follow-up or regular screening after initial detection for discrimination of lung cancer. Volume doubling time (AUC: 0.915, 95%CI 0.862-0.967, P<0.0001); Volume (AUC: 0.871, 95%CI 0.818-0.925, P<0.0001); Simulated mean diameter (AUC: 0.822, 95%CI 0.748-0.897, P<0.0001); Volume doubling time and ≥200mm^3 criterion (AUC: 0.939, 95%CI 0.903-0.975, P<0.0001). AUC=area under the curve.

*Exact volume measurement or simulated mean diameter was not available for 60 benign nodules and one lung cancer, and they were not included in the calculations. Diameters were simulated from computer generated volume measurements, based on three-dimensional voxels. Manually measured diameters are less accurate and will overestimate nodule size.

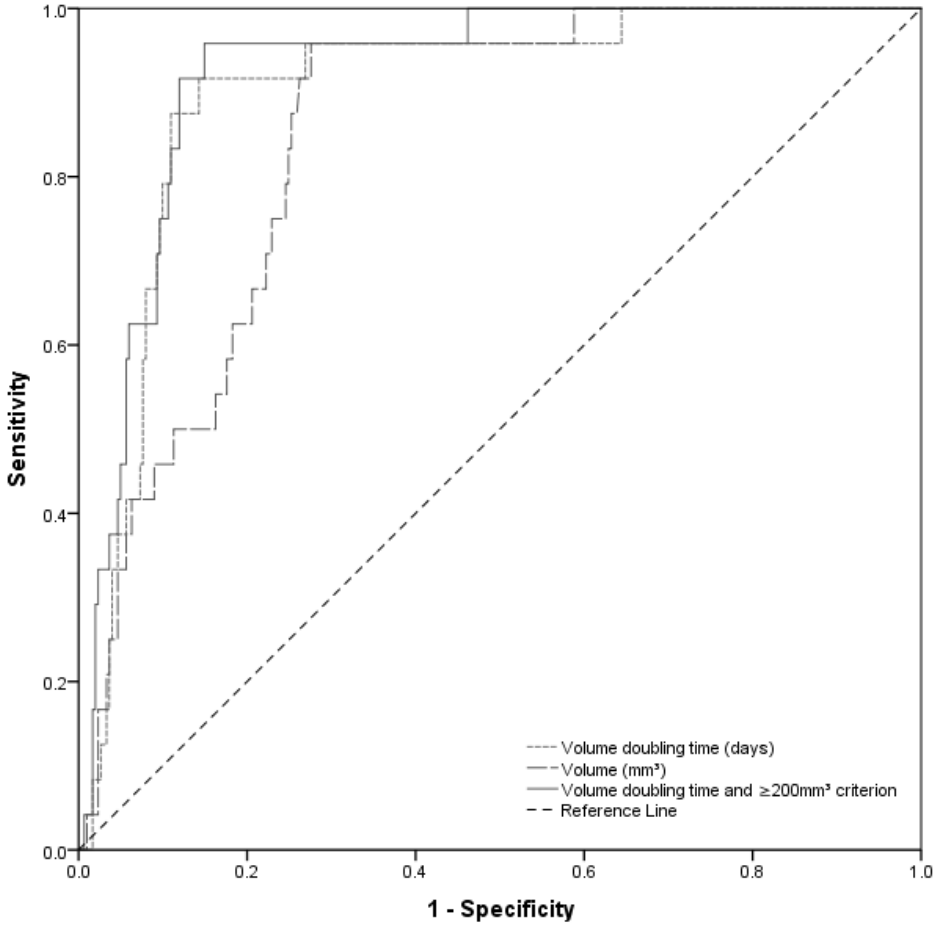

Figure S3: Participant level: Receiver operating characteristic curves* of fastest volume doubling time, largest nodule volume, and the combination of fastest volume doubling time and ≥200mm^3 largest nodule volume criterion at first follow-up or regular screening after initial detection for discrimination of lung cancer. Volume doubling time (AUC: 0.901, 95%CI 0.846-0.956, P<0.0001); Volume (AUC: 0.849, 95%CI 0.790-0.908, P<0.0001); Volume doubling time and ≥200mm^3 (AUC: 0.923, 95%CI 0.881-0.965, P<0.0001). AUC=area under the curve.

* Exact volume measurement was not available for 34 benign nodules and one cancer, and they were not included in the calculations.

Supplementary Tables

Table S1: Characteristics of included participants with at least one new solid nodule during second or third screening round and subsequent follow-up or regular screening (n=680)

		At least one new nodule persisted at follow-up		
	Overall Population, n=680 (100%)	**Yes, n=359[*] (52.8%)**	**No, n=321 (47.2%)**	**P-Value**
Sex				0.246
Female	166/680 (24.4)	81/359 (22.6)	84/321 (26.3)	
Male	514/680 (75.6)	278/359 (77.4)	236/321 (73.8)	
Age (years)				
50 - 54	158/680 (23.2)	87/359 (24.2)	71/321 (22.1)	
55 - 59	209/680 (30.7)	111/359 (30.9)	98/321 (30.5)	
60 - 64	185/680 (27.2)	92/359 (25.6)	93/321 (29.0)	
65 - 69	91/680 (13.4)	47/359 (13.1)	44/321 (13.7)	
≥70	37/680 (5.4)	22/359 (6.1)	15/321 (4.7)	
Median (IQR)	59 (55-63)	59 (55-63)	59 (55-63)	0.811
Smoking pack-years[‡]				
<20	2/679 (0.3)	1/358 (0.3)	1/321 (0.3)	
20 - 39	380/679 (56.0)	208/358 (57.9)	172/321 (53.6)	
40 - 59	208/678 (30.6)	102/358 (28.5)	106/321 (33.0)	
60 - 79	57/679 (8.4)	28/358 (7.8)	29/321 (9.0)	
≥80	32/679 (4.7)	19/358 (5.3)	13/321 (4.0)	
Median (IQR)	39 (30-49)	39 (30-49)	39 (30-49)	0.482

Abbreviations: IQR - Interquartile range.

[*] In four participants a benign new solid nodule changed to part-solid (n=3) or pure ground-glass nodules (n=1) at follow-up. In three participants the respective nodule was the only new solid nodule detected.
[‡] Pack-Year information was missing for one participant.

Table S2: New solid nodules at initial detection stratified by volume (N=1020; 995 benign nodules and 25 lung cancer nodules)

	All new solid nodules, n=1020 (100%)	**New solid not visible in retrospect, n=788 (77%)**	**New solid nodules below the trial's detection limit in retrospect, n=232 (33%)**
<50mm^3			
All nodules	618/1020 (61%)	394/788 (50%)	224/232 (97%)
% Lung cancer	9/618 (2%)	6/394 (2%)	3/224 (1%)
Nonresolving nodules	284/618 (46%)	108/394 (27%)	176/224 (79%)
% Lung cancers	9/284 (3%)	6/108 (6%)	3/176 (2%)
50-<500mm^3			
All nodules	361/1020 (35%)	354/788 (45%)	7/232 (3%)
% Lung cancer	16/361 (4%)	15/354 (4%)	1/7 (14%)
Nonresolving nodules	158/361 (44%)	153/354 (43%)	5/7 (71%)
% Lung cancers	16/158 (10%)	15/153 (10%)	1/5 (20%)
≥500mm^3			
All nodules	38/1020 (4%)	37/788 (5%)	1/232(<1%)
% Lung cancer	0/38 (0%)	0/37 (0%)	0/1 (0%)
Nonresolving nodules	15/38 (34%)	14/37 (38%)	1/1 (100)
% Lung cancers	0/15 (0%)	0/37 (0%)	0/1 (0%)

Table S3: Characteristics of included participants with at least one new solid nodule during second or third screening round that persisted as solid nodule after initial detection.*

	Overall Population, n=356 (100%)	Lung Cancer		P-Value
		Yes, n=25 (7.0%)	No, n=331 (93.0%)	
Sex				0.999
Female	80/356 (22.5)	5/25 (20.0)	75/331 (22.7)	
Male	276/356 (77.5)	20/25 (80.0)	256/331 (77.3)	
Age (years)				
50 - 54	87/356 (24.2)	7/25 (28.0)	79/331 (23.9)	
55 - 59	110/356 (30.9)	5/25 (20.0)	105/331 (31.7)	
60 - 64	92/356 (25.8)	5/25 (20.0)	87/331 (26.3)	
65 - 69	46/356 (12.9)	6/25 (24.4)	40/331 (12.1)	
≥70	22/356 (6.2)	2/25 (8.0)	20/331 (6.0)	
Median (IQR)	59 (55-63)	60 (54-65)	58 (55-63)	0.393
Smoking pack-years†				
<20	1/355 (0.3)	0	1/330 (0.3)	
20 - 39	208/355 (58.4)	12/25 (48.0)	196/330 (59.4)	
40 - 59	101/355 (28.4)	9/25 (36.0)	92/330 (27.9)	
60 - 79	27/355 (7.6)	3/25 (12.0)	24/330 (7.3)	
≥80	18/355 (5.1)	1/25 (4.0)	17/330 (5.2)	
Median (IQR)	39 (30-49)	44 (30-55)	38 (30-49)	0.350

Abbreviations: IQR - Interquartile range.

* In three (<1% [3/359]) of the participants the new nodule did not persist as solid nodule and they were excluded from the calculations.
† Pack-Year information was missing for one participant.

Table S4: Histology and staging of the 25 lung cancers

	Adenocarcinoma, 16/25 (64%)	Large cell carcinoma, 3/25 (12%)	Squamous cell carcinoma, 2/25 (8%)	Others*, 4/25 (16%)
Stage				
I	15 (94%)	2 (67%)	2 (100%)	4 (100%)
III	1 (6%)	1 (33%)	0	0

* Others included one large cell neuro-endocrine carcinoma, one non-small-cell lung carcinoma not otherwise specified, and two lung cancers where the histological diagnosis could not be established.

Table S5: Performance of predefined VDT cutoffs at first follow-up or regular screening after initial detection (N=437; 412 benign nodules and 25 lung cancer nodules)

	All new solid nodules that persisted on the first LDCT after detection	Subsequent LDCT within 120 days	Subsequent LDCT after 120 days
Lung cancer probability			
VDT >600 days (95% CI)	2/361, 0.6% (0-2.1)	2/139, 1.4% (0.1-5.4)	0/222, 0 % (0-2.0)
VDT 400-600 days (95% CI)	1/12, 8.3% (0-37.5)	0/3, 0% (0-61.7)	1/9, 11.1% (0-45.7)
VDT <400 days (95% CI)	22/64, 34.4% (23.9-46.6)	15/53, 28.3% (17.9-41.7)	7/11, 63.6% (35.2-85.0)
VDT <400 days			
Sensitivity (95% CI)	22/25, 88.0% (69.2-96.7)	15/17, 88.2% (64.4-98.0)	7/8, 87.5% (50.8-99.9)
Specificity (95% CI)	370/412, 89.8% (86.5-92.4)	140/178, 78.7% (72.0-84.1)	230/234, 98.3% (95.5-99.5)
PPV (95% CI)	22/64, 34.4% (23.9-46.6)	15/53, 28.3% (17.9-41.7)	7/11, 63.6% (35.2-85.0)
NPV (95% CI)	370/373, 99.2% (97.5-99.8)	140/142, 98.6% (94.7-99.9)	230/231, 100% (97.3-100)
VDT <600 days			
Sensitivity (95% CI)	23/25, 92.0% (73.9-98.9)	15/17, 88.2% (64.4-98.0)	8/8, 100% (62.8-100)
Specificity (95% CI)	359/412, 87.1 % (83.5-90.0)	137/178, 77.0% (70.2-82.6)	222/234, 94.9% (91.7-97.4)
PPV (95% CI)	23/76, 30.3% (21.0-41.4)	15/56, 26.8% (17.5-41.0)	8/20, 40.0% (21.8-61.4)
NPV (95% CI)	359/361, 99.4% (97.9-100)	137/139, 98.6% (94.6-99.9)	222/222, 100% (98.0-100)
VDT ≤590 days or volume ≥200mm³	25/25, 100.0% (84.2-100)	17/17, 100.0% (78.4-100)	8/8, 100% (62.8-100)
Sensitivity (95% CI)	345/412, 83.7% (79.9-87.0)	124/178, 69.7% (62.5-76.0)	221/234, 94.4% (90.6-96.8)
Specificity (95% CI)	25/92, 27.2% (19.1-37.1)	17/71, 24.6% (15.9-36.0)	8/21, 38.1% (20.7-59.2)
PPV (95% CI)	345/345, 100.0% (98.7-100)	124/124, 100.0% (96.4-100)	221/221, 100.0% (97.9-100)
NPV (95% CI)			

Abbreviations: IQR - Interquartile range, LDCT – Low-dose computed tomography, NPV - Negative predictive value, PPV - Positive predictive value, VDT - Volume doubling time.
Exact volume measurement was not available or classification based on radiologist's size categorization was unattainable for 17 benign nodules, and they were not included in the calculations.

Table S6: Performance of identified cutoffs for new solid nodules stratified by their visibility in retrospect (N=437; 412 benign nodules and 25 lung cancer nodules)

	New solid nodules at initial detection not visible in retrospect	New solid nodules at initial detection visible in retrospect as minuscule nodule below the trial's detection limit
VDT ≤590 days		
Sensitivity (95% CI)	19/21, 90.5 (69.9-98.6)	4/4, 100% (44.4-100)
Specificity (95% CI)	191/236, 80.9% (75.4-85.5)	169/176, 96.0% (91.9-98.2)
PPV (95% CI)	19/64, 29.7% (19.8-41.8)	4/11, 36.4% (15.0-64.8)
NPV (95% CI)	191/193, 99.0% (96.1-100)	169/169, 100% (97.3-100)
VDT ≤590 days or volume ≥200mm^3		
Sensitivity (95% CI)	21/21, 100% (81.8-100)	4/4, 100% (44.4-100)
Specificity (95% CI)	174/232, 74.6% (68.6-79.7)	169/176, 96.0% (91.9-98.2)
PPV (95% CI)	21/79, 25.9% (17.6-36.5)	4/11, 36.4% (15.0-64.8)
NPV (95% CI)	176/176, 100.0% (97.4-100)	169/169, 100% (97.3-100)
Volume ≥65mm^3		
Sensitivity (95% CI)	21/21, 100% (81.8-100)	3/4, 75% (28.9-96.6)
Specificity (95% CI)	141/236, 59.7% (53.4-65.8)	172/176, 97.7% (94.1-99.3)
PPV (95% CI)	21/116, 18.1% (12.1-26.2)	3/7, 42.9% (15.8-75.0)
NPV (95% CI)	141/141, 100% (96.8-100)	172/173, 99.4% (96.5-100)

Abbreviations: IQR - Interquartile range, NPV - Negative predictive value, PPV - Positive predictive value, VDT - Volume doubling time.
Exact volume measurement or simulated mean diameter was not available and classification based on the radiologist's size categorization was unattainable for 17 benign nodules, and they were not included in the calculations.

Table S7: Performance of identified cutoffs at first follow-up or regular screening after initial detection for nodules with simulated mean diameter classification available (N=432; 407 benign nodules and 25 lung cancer nodules)

	All new solid nodules that persisted on the first LDCT after detection	Subsequent LDCT within 120 days	Subsequent LDCT after 120 days
VDT ≤590 days			
Sensitivity (95% CI)	23/25, 92.0% (73.9-98.9)	15/17, 88.2% (64.4-98.0)	8/8, 100% (62.8-100)
Specificity (95% CI)	357/407, 87.7% (84.1-90.6)	135/174, 77.6% (70.8-83.2)	222/233, 95.3% (91.7 -97.4)
PPV (95% CI)	23/73, 31.5% (22.0-42.9)	15/54, 27.8% (17.5-41.0)	8/19, 42.1% (23.1-63.8)
NPV (95% CI)	357/359, 99.4% (97.9-100)	135/137, 98.5% (94.5-99.9)	222/222, 100% (98.0-100)
VDT ≤590 days or volume ≥200mm^3	25/25, 100.0% (84.2-100)	17/17, 100.0% (78.4-100)	8/8, 100% (62.8-100)
Sensitivity (95% CI)	342/407, 84.0% (80.1-87.3)	122/174, 70.1% (62.9-76.4)	220/233, 94.4% (90.6-96.8)
Specificity (95% CI)	25/75, 27.8% (19.5-37.8)	17/69, 24.6% (15.9-36.0)	8/21, 38.1% (20.7-59.2)
PPV (95% CI)	342/342, 100.0% (98.7-100)	122/122, 100.0% (96.3-100)	220/220, 100.0% (97.9-100)
NPV (95% CI)			
Volume ≥65mm^3			
Sensitivity (95% CI)	24/25, 96.0% (78.9-100)	16/17, 94.1% (71.1-100)	8/8, 100% (62.8-100)
Specificity (95% CI)	311/407, 76.4% (72.0-80.3)	93/174, 53.4% (46.0-60.7)	218/233, 93.6% (89.6-96.1)
PPV (95% CI)	24/120, 20.0% (13.8-28.1)	16/97, 16.5% (10.3-25.2)	8/23, 34.8% (18.7-55.2)
NPV (95% CI)	311/312, 99.7% (98.0-100)	93/94, 98.9% (93.6-100)	218/218, 100% (97.9-100)
Simulated mean diameter ≥5mm	24/25, 96.0% (78.9-100)	16/17, 94.1% (71.1-100)	8/8, 100% (62.8-100)
Sensitivity (95% CI)	284/407, 69.8% (65.1-74.0)	76/174, 43.7% (36.5-51.1)	208/233, 89.3% (84.6-92.7)
Specificity (95% CI)	24/147, 16.3% (11.2-23.2)	16/114, 14.0% (8.7-21.7)	8/33, 24.2% (12.6-41.3)
PPV (95% CI)	284/285, 99.6% (97.8-100)	76/77, 98.7% (92.3-100)	208/208, 100% (97.8-100)
NPV (95% CI)			

Abbreviations: IQR - Interquartile range, LDCT – Low-dose computed tomography, NPV - Negative predictive value, PPV - Positive predictive value, VDT - Volume doubling time.
Exact volume measurement or simulated mean diameter was not available and classification based on the radiologist's size categorization was unattainable for 22 benign nodules, and they were not included in the calculations.

Table S8: Lung cancer probability for participants with at least one persisting new solid nodule stratified by volume doubling time and volume at of the largest or fastest-growing new solid nodule at first follow-up of regular screening after initial detection

	Participants with lung cancer/participants meeting criterion	Lung cancer probability (95% CI)
VDT		
>590 days	2/269	0.7% (0.0-2.8)
≤590 days	23/71	32.4% (22.6-44.0)
Volume		
<65mm^3	1/228	0.4% (0.0-2.7)
≥65mm^3	24/112	24/112, 21.4% (14.8-30.0)
VDT and volume		
>590 days and <200mm^3	0/253	0.0% (0.0-1.8)
≤590 days or ≥200mm^3	25/91	27.5% (19.3-37.5)

Abbreviations: CI - Confidence interval, IQR - Interquartile range, VDT - Volume doubling time.
In 14 participants without lung cancer insufficient nodule size data led to their exclusion from the analysis.

Table S9: Performance of identified cutoffs in participants based on the largest or fastest-growing new solid nodule at first follow-up or regular screening after initial detection

	All new solid nodules that persisted on the first LDCT after detection
VDT ≤590 days	
Sensitivity (95% CI)	23/25, 92.0% (73.9-98.9)
Specificity (95% CI)	267/315, 84.8% (80.4-88.3)
PPV (95% CI)	23/71, 32.4% (22.6-44.0)
NPV (95% CI)	267/269, 99.3% (97.2-100)
VDT ≤590 days or volume ≥200mm^3	
Sensitivity (95% CI)	25/25, 100.0% (84.2-100)
Specificity (95% CI)	253/315, 80.3% (75.6-84.3)
PPV (95% CI)	25/87, 28.7% (20.2-39.0)
NPV (95% CI)	253/253, 100.0% (98.2 -100)
Volume ≥65mm^3	
Sensitivity (95% CI)	24/25, 96.0% (78.9-100)
Specificity (95% CI)	227/315, 72.1% (66.9-76.7)
PPV (95% CI)	24/112, 21.4% (14.8-30.0)
NPV (95% CI)	313/314, 99.6% (97.4-100)

Abbreviations: IQR - Interquartile range, LDCT – Low-dose computed tomography, NPV - Negative predictive value, PPV - Positive predictive value, VDT - Volume doubling time.
In 14 participants without lung cancer insufficient nodule size data led to their exclusion from the analysis.

Supplementary References

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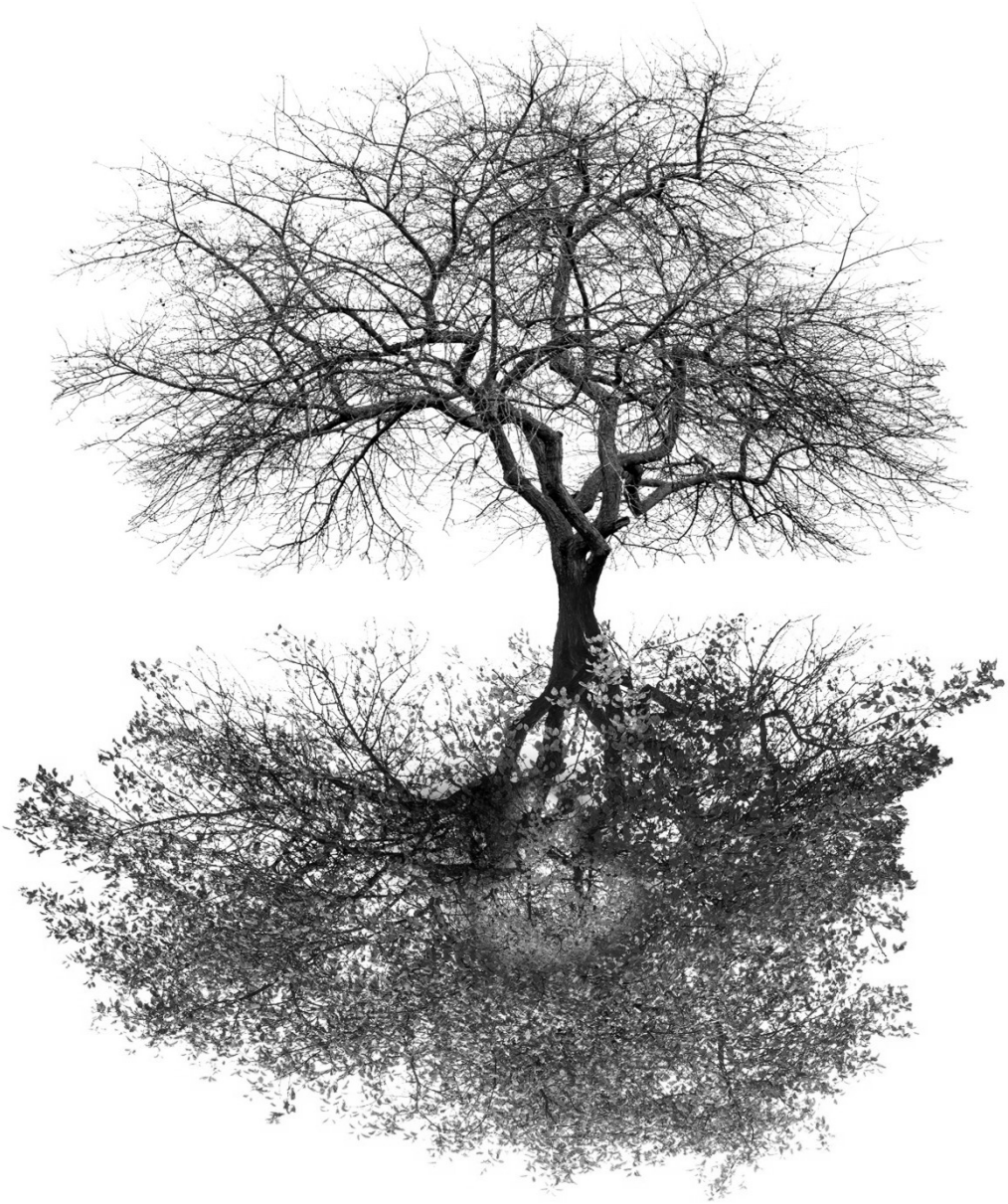

Chapter 6

Characteristics of new solid nodules detected in incidence screening rounds of low-dose CT lung cancer screening

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ABSTRACT

PURPOSE: New nodules after baseline are regularly found in low-dose CT lung cancer screening and have a high lung cancer probability. It is unknown whether morphological and location characteristics can improve new nodule risk stratification by size.

METHODS: Solid non-calcified nodules detected during incidence screening rounds of the randomised controlled Dutch-Belgian lung cancer screening (NELSON) trial and registered as new or previously below detection limit (15 mm^3) were included. A multivariate logistic regression analysis with lung cancer as outcome was performed, including previously established volume cut-offs (<30 mm^3, 30-<200 mm^3 and ≥200 mm^3) and nodule characteristics (location, distribution, shape, margin and visibility <15 mm^3 in retrospect).

RESULTS: Overall, 1280 new nodules were included with 73 (6%) being lung cancer. Of nodules ≥30 mm^3 at detection and visible <15 mm^3 in retrospect, 22% (6/27) were lung cancer. Discrimination based on volume cut-offs (area under the receiver operating characteristic curve (AUC): 0.80, 95% CI 0.75 to 0.84) and continuous volume (AUC: 0.82, 95% CI 0.77 to 0.87) was similar. After adjustment for volume cut-offs, only location in the right upper lobe (OR 2.0, P=0.012), central distribution (OR 2.4, P=0.001) and visibility <15 mm^3 in retrospect (OR 4.7, P=0.003) remained significant predictors for lung cancer. The Hosmer-Lemeshow test (P=0.75) and assessment of bootstrap calibration curves indicated adequate model fit. Discrimination based on the continuous model probability (AUC: 0.85, 95% CI 0.81 to 0.89) was superior to volume cut-offs alone, but when stratified into three risk groups (AUC: 0.82, 95% CI 0.78 to 0.86), discrimination was similar.

CONCLUSION: Contrary to morphological nodule characteristics, growth-independent characteristics may further improve volume-based new nodule lung cancer prediction, but in a three-category stratification approach, this is limited

Introduction

Lung cancer remains as a leading cause of cancer-related death worldwide, and US guidelines recommend lung cancer screening by low-dose CT (LDCT) for high-risk individuals.[1–5] Presently, lung cancer screening guidelines and nodule management protocols primarily focus on size and nodule growth for risk stratification, but the potential incremental value of morphological and location nodule characteristics has been underlined.[6–11] It has been reported that nodules smaller than 5–6 mm (roughly 65–113 mm^3) have a very low likelihood of being lung cancer.[8,10,12,13] However, current knowledge concerning nodule management in lung cancer screening is mainly based on baseline nodules that may have been present for years before their detection.[14,15] New nodules after baseline develop within a known timeframe and entail a group of young and potentially fast-growing nodules. Recently, the Dutch-Belgian lung cancer screening trial (NELSON) published a more detailed analysis on new nodules detected in incidence screening rounds.[14] It was shown that compared with baseline nodules, new solid nodules possess a greater lung cancer probability already at smaller size,[13,14] and subsequent data from the National Lung Cancer Screening Trial indicated similar findings.[16] Furthermore, it has been suggested that participants with new nodule lung cancer have poorer survival outcomes compared with participants who had at least one positive screen prior to cancer diagnosis.[17] Based on the results in the NELSON trial, it was proposed in an European position statement on lung cancer screening that new solid nodules identified at an incidence screen and <30 mm^3 volume (adapted from 27 mm^3, <1% lung cancer probability) or <4 mm (simulated mean) diameter (adapted from 3.7 mm, <1% lung cancer probability) comprise low risk nodules, new solid nodules 30–<200 mm^3 (adapted from 206 mm^3, around 3% lung cancer probability) or 4–8 mm (simulated mean) diameter (adapted from 8.2 mm, around 3% lung cancer probability) represent indeterminate risk nodules and new solid nodules ≥200 mm^3 (around 17% lung cancer probability) or ≥8 mm (simulated mean) diameter (around 14% lung cancer probability) are high-risk nodules, which was also adopted in the British Thoracic Society Guidelines for the Investigation and Management of Pulmonary Nodules.[11,14]

In the clinical setting, physicians evaluate solid pulmonary nodules based on their size and based on their morphological and location characteristics, and likewise in lung cancer screening, the expertise of a radiologist was shown to decrease false-

positive screen results.[9 18 19] Nodule location in the upper lung and right upper lung in particular as well as marginal spiculation have been typically identified as risk factor for lung cancer in screening studies.[10,16,20–22] Nevertheless, consistent characterisation of very small nodules can be challenging and evidence concerning the discriminative value of new nodule morphology and location for lung cancer in new nodules in incidence screening rounds of LDCT screening is lacking.

The aim of this study was to assess whether addition of morphological and location characteristics to currently proposed volume-based three-category risk stratification can improve management of new solid nodules in LDCT lung cancer screening.

Methods

Study population

The NELSON trial was authorised by the Dutch Health Care Committee. All participants provided written informed consent. The recruitment process and study design were published before.[7,23,24] Summarised, eligible patients were adults aged 50–75 years, who had smoked >15 cigarettes per day for >25 years or >10 cigarettes per day for >30 years and were still smoking or stopped smoking <10 years previously. Between April 2004 and December 2006, 7557 participants underwent baseline screening in four centres in the Netherlands and Belgium. The incidence screening rounds took place 1 year, 3 years and 5.5 years after baseline screening. In this study, participants with a solid non-calcified nodule detected during the incidence screening rounds and registered by the NELSON radiologists as new or <15 mm^3 (study detection limit) at previous screens were included.

CT scanning protocol

The CT protocol was published before.[7,24] The four screening sites used 16-MDCT scanners or 64-MDCT scanners (Sensation-16, Siemens Medical Solutions, Forchheim, Germany, or Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Best, The Netherlands). Scans of the entire chest were performed without contrast in spiral mode in caudio-cranial direction with 16×0.75 mm collimation and 1.5 pitch. Low dose settings (80–90 kVp, 120 kVp and 140 kVp) were adjusted depending on body weight (<50 kg, 50–80 kg or >80 kg), matching a CT dose index volume of 0.8 mGy, 1.6 mGy

or 3.2 mGy, respectively. Datasets were derived from images of the thorax with 1.0 mm slice width and a 0.7 mm reconstruction interval. Screening conditions and data acquisition were standard across screening sites.[7,24]

Image reading

In the first two rounds, two independent radiologists with experience in thoracic CT reading ranging between 1 year and 20 years evaluated each CT scan individually, and in case of discrepancy, a third reader made the final decision.[7,24] In the third and fourth screening rounds, single read was performed by radiologists with at least 6 years of experience in thoracic imaging after it was shown that double reading consensus has no benefit when using semiautomated software.[25] CT data analysis was performed on digital workstations (Leonardo, Siemens Medical Solutions) using software for semiautomated volume measurements (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions). Lung windows were assessed at a width of 1600 HU and a level of −700 HU. All images were interpreted both in lung window and mediastinal settings.

A non-calcified nodule was considered solid if the underlying structures were completely obscured by its lung opacity. A nodule's shape was classified as spherical, polygonal or irregular.[19] The nodule margin was classified as smooth, lobulated, spiculated or irregular.[21,26]Additional to the nodule location in the lung, the distribution (peripheral and central) within the lung parenchyma was characterised based on the distance to the costal pleura. If the distance to costal pleura was less than one-third of the total distance to hilum-costal pleura, the nodule was defined as peripheral and if it was more than one-third, the nodule was defined as central.[19,27] After detection, the software's matching algorithm matched nodules individually (depending on consistency, size and location) with previous scans and the radiologists visually confirmed the matching. In this analysis, a nodule was considered new if it was registered by the radiologist as new or below the study detection limit of 15 mm^3 on the previous scan. Radiologists could overrule protocol-based screening result (done for 195 (6%) of 3318 participants at the baseline screening round) in case of high suspicion of malignancy (eg, enlarged mediastinal lymph nodes) or benignity (eg, benign calcification patterns) and to adjust the volume measurement in case of inappropriate segmentation.[18] Data obtained during CT evaluation were directly uploaded to the NELSON management system.[7] For this study, nodule information as

reported by the radiologists in the NELSON management system was used, and no retrospective measurements was performed.

Nodule management protocol

The NELSON nodule management protocol has been described in detail previously.[7] Summarised, solid nodules detected within the NELSON trial were classified into four categories (NODCAT I–IV) according to their size and benign characteristics. After baseline screening, calcified nodules or nodules with other benign characteristics were considered benign (NODCAT I), new solid nodules without benign characteristics measuring 15–50 mm^3 (NODCAT II, follow-up LDCT within 1 year) and new solid nodules 50–500 mm^3(NODCAT III, follow-up LDCT within 6–8 weeks) were defined indeterminate, whereas nodules measuring ≥500 mm^3 (NODCAT IV, immediate referral to pulmonologist) were considered positive. After initial detection, a nodule's subsequent evaluation was based on volume doubling time.[7] A volume doubling time <400 days led to referral to a pulmonologist for further diagnosis.

Outcomes

For this study, a nodule was classified as lung cancer when it was diagnosed as lung cancer during diagnostic workup according to national and international guidelines including histological examination.[7] Nodules were classified as benign when either: (A) the nodule was benign at histological examination; (B) extensive diagnostic evaluation had a negative finding; (C) the nodule was ruled negative during the participant's last follow-up screening of the NELSON trial and the participant did not present with postscreening lung cancer according to the Dutch and Belgian national cancer registries and medical file review.[7 13 28]

Previously established volume cut-offs for new nodules at initial detection

Considering a previous analysis of the first two incidence screening rounds of the NELSON trial concerning optimal new nodule volume cut-offs at initial detection,[14] nodules were classified as <30 mm^3 (low risk), 30–<200 mm^3 (intermediate risk) or ≥200 mm^3 (high risk) based on their semiautomated volume measurements (continuous volume) or the radiologist's nodule classification (<50 mm^3, 50–500 mm^3, >500 mm^3; performed for 4% (50/1280) of the included nodules).[11]

Statistical analysis

The normality assumption was tested using the Kolmogorov-Smirnov test as well as visual assessment. Continuous variables are presented as median and IQR, and categorical variables are presented as frequencies and respective percentages. CIs of proportions were calculated using the Agresti-Coull method. The Mann-Whitney U test was used to compare the nodule volume of benign nodules and lung cancers at initial detection. Nominal variables were analysed with Fisher's exact test. Logistic regression analysis with new nodule lung cancer as outcome was performed to assess morphological and location nodule characteristics together with the previously established new nodule volume cut-offs (<30 mm^3, 30–<200 mm^3 and ≥200 mm^3)[11,14]. The final parsimonious model included nodule characteristics that were significant ($P<0.05$) for new nodule lung cancer when adjusted for the volume cut-offs. The model calibration was assessed using the Hosmer-Lemeshow goodness-of-fit test and bootstrap calibration plots of actual probability versus predicted probability, with ideal, apparent and bias-corrected curves. The model probability was stratified through assessment of Youden Indices to maximise the area under the receiver operating characteristic curve (AUC) for three categories (termed low risk, intermediate risk and high risk) and provide at least 95% sensitivity, analogous to the previously established volume cut-offs.[14] The performance for discriminating new nodule lung cancer was quantified by the AUC. The model performance was internally validated using 10-fold cross-validation. AUC comparison was performed with the method described by DeLong *et al*.[29] Decision curve analysis was used to estimate clinical usefulness of the model by plotting the net benefit (y-axis) over a continuum of potential decision probability thresholds (x-axis).[30,31] The net benefit represents the sum of true-positive minus false-positive classifications weighted by the respective probability threshold (eg, a decision threshold of 10% would imply that for every true-positive classification nine false-positive classifications are clinically acceptable). Missing data were excluded from the respective analyses. Statistical analyses were performed with SPSS V.25.0 (IBM, Armonk, USA), R V.3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington, USA).

Results

In total, 1280 new solid nodules detected in 809 participants during the three incidence rounds were included (figure 1).

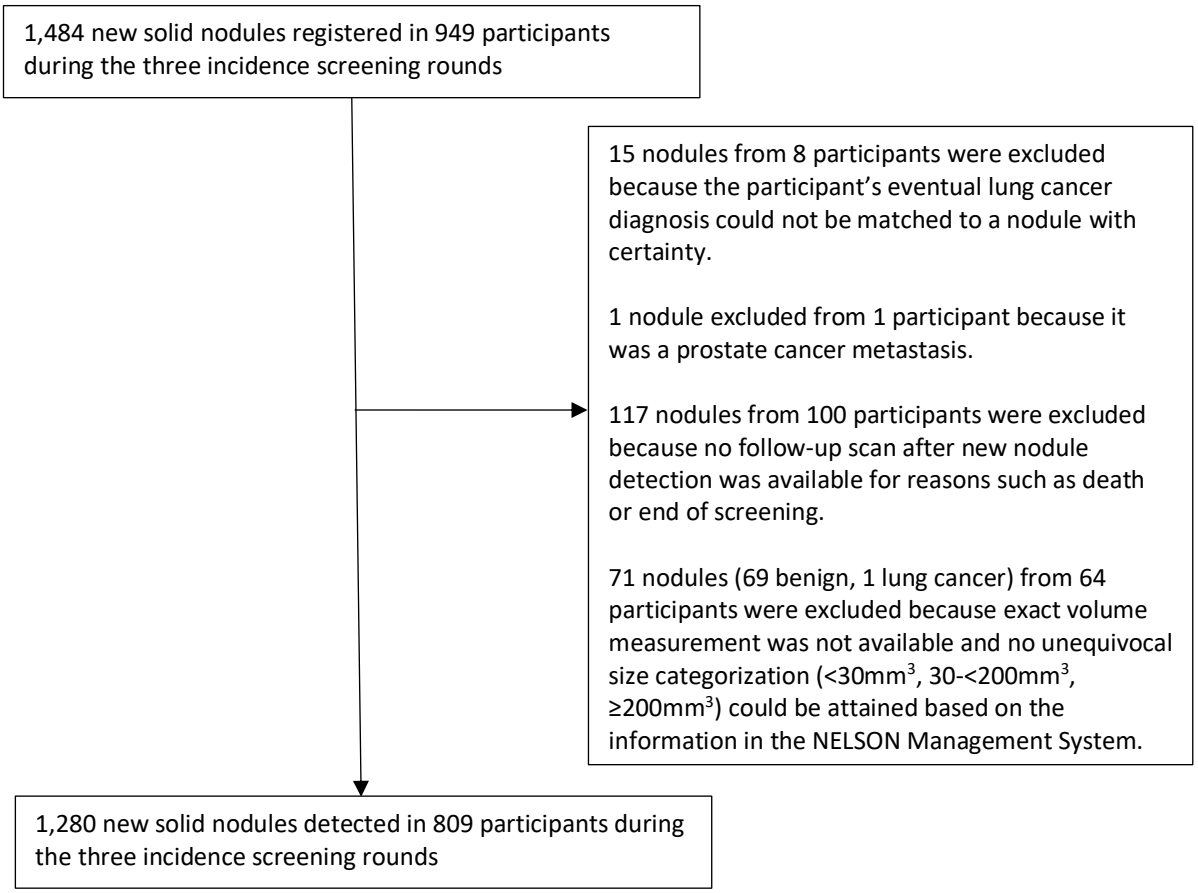

Figure 1: Flowchart of new solid nodules included in this analysis.

Median participant age at baseline screening was 59 years (IQR 55–63 years), and 77% (622/809) were male. Of the included nodules, 20% (255/1280) were visible as small nodule <15 mm^3 in retrospect. Eventually, 6% (73/1280) of the new solid nodules were diagnosed as lung cancer. At initial detection, median nodule volume was 50 mm^3(IQR 23–156 mm^3) with 34% (429/1280) being <30 mm^3, 43% (547/1280) being 30–<200 mm^3 and 24% (304/1280) being ≥200 mm^3.

Table 1 presents the nodule characteristics of benign new solid nodules and lung cancers at initial nodule detection and the proportion of lung cancers stratified by the volume cut-offs. Overall, new solid nodules visible in retrospect <15 mm^3 were smaller

and less often lung cancer compared with new solid nodules not visible in retrospect (3% (8/255) vs 6% (65/1025)). However, of new solid nodules ≥30 mm^3 at detection and visible <15 mm^3 in retrospect, 22% (6/27) were lung cancer compared with 8% (65/824) of new solid nodules ≥30 mm^3 and not visible in retrospect. Table 2 displays the results of the logistic regression analysis. Larger volume, location in the right upper lung, central distribution, irregular shape and a lobulated or spiculated margin were associated with lung cancer in univariate analysis. After addition of the volume cut-off categories to the selected nodule characteristics by multivariate logistic regression, only location in the right upper lung and central distribution significantly improved lung cancer prediction. Furthermore, after addition of the volume cut-offs, visibility in retrospect as small nodule <15 mm^3 was significantly associated with lung cancer. In other words, at equivalent size a new solid nodule visible in retrospect <15 mm^3 was more likely lung cancer than a new nodule not visible at all. The full model included the nodule volume cut-offs, location in the lung, distribution in the lung and visibility in retrospect

		Lung cancer			Proportion of nodules with characteristic being lung cancer		
	Overall, 100% (N=1280)	No, 94% (N=1207)	Yes, 6% (N=73)	P Value	<30mm^3, 33% (N=429)	30-<200mm^3, 43% (N=547)	≥200mm^3, 24% (N=304)
Nodule volume					0.5 (2/429)	3 (18/547)	17 (53/304)
<30mm^3	34 (429/1280)	35 (427/1207)	3 (2/73)	<0.0001	-	-	-
30-<200mm^3	43 (547/1280)	44 (529/1207)	25 (18/73)	0.001	-	-	-
≥200mm^3	24 (304/1280)	21 (251/1207)	73 (53/73)	<0.0001	-	-	-
Median (mm^3) (IQR)	50 (23-156)	47 (22-132)	387 (124-1017)	<0.0001	-	-	-
Location							
Right upper lung	26 (327/1277)	25 (299/1204)	38 (28/73)	0.013	2 (2/100)	5 (7/155)	26 (19/72)
Left upper lung	21 (273/1277)	22 (259/1204)	19 (14/73)	0.769	0 (0/94)	4 (5/122)	16 (9/57)
Right lower lung	33 (424/1277)	34 (207/1204)	23 (17/73)	0.073	0 (0/143)	1 (2/166)	13 (15/115)
Left lower lung	20 (253/1277)	20 (239/1204)	19 (14/73)	1.000	0 (0/92)	4 (4/103)	17 (10/58)
Right or left lung							
Right lung	59 (751/1277)	59 (706/1204)	62 (45/73)	0.714	1 (2/243)	3 (9/321)	18 (34/187)
Left lung	41 (526/1277)	41 (498/1204)	38 (28/73)	0.714	0 (0/186)	4 (9/225)	17 (19/115)
Distribution							
Central	22 (281/1272)	21 (255/1199)	36 (26/73)	0.008	0 (0/87)	6 (8/134)	30 (18/60)
Peripheral	78 (991/1272)	79 (944/1199)	64 (47/73)	0.008	1 (2/341)	2 (10/410)	15 (35/240)
Shape							
Round	56 (638/1137)	57 (613/1076)	41 (25/61)	0.017	0.3 (1/311)	2 (4/255)	28 (20/72)
Polygonal	35 (400/1137)	35 (378/1076)	36 (22/61)	0.891	1 (1/94)	4 (8/204)	13 (13/102)
Irregular	9 (99/1137)	8 (85/1076)	23 (14/61)	0.0004	0 (0/2)	5 (1/20)	17 (13/77)
Margin							
Smooth	53 (671/1260)	55 (656/1189)	21 (15/71)	<0.0001	0.3 (1/390)	3 (7/244)	19 (7/37)
Lobulated	36 (453/1260)	35 (417/1189)	51 (36/71)	0.010	0 (0/32)	4 (10/272)	17 (26/149)
Spiculated	7 (82/1260)	6 (68/1189)	20 (14/71)	<0.0001	0 (0/2)	0 (0/12)	21 (14/68)
Irregular	4 (54/1260)	4 (48/1189)	9 (6/71)	0.119	33 (1/3)	0 (0/12)	13 (5/39)
Visibility in retrospect							
Not visible	80 (1025/1280)	80 (960/1207)	89 (65/73)	0.050	0 (0/201)	3 (14/528)	17 (51/296)
Small nodule <15mm^3	20 (255/1280)	20 (247/1207)	11 (8/73)	0.050	1 (2/228)	21 (4/19)	25 (2/8)

Table 1: Nodule characteristics of benign nodules and lung cancers
Abbreviations: IQR - Interquartile range. Missing values were excluded from analyses.

	Univariate analysis		Volume cutoffs added to each characteristic		Full model		
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value	Beta coefficient
Volume cutoff values							
<30mm^3	Reference				Reference		
30-<200mm^3	7.3 (1.7-31.5)	0.008			16.8 (3.2-85.4)	0.001	2.818
≥200mm^3	45.1 (10.9-186.6)	<0.0001			128.1 (25.1-651.9)	<0.0001	4.852
Location							
Right upper lung	1.9 (1.2-3.1)	0.011	2.1 (1.3-3.5)	0.005	2.0 (1.2-3.4)	0.012	0.687
Not right upper lung	Reference		Reference		Reference		
Right or left lung							
Right lung	1.1 (0.7-1.8)	0.613	1.0 (0.6-1.7)	0.904			
Left lung	Reference		Reference				
Distribution							
Central	2.0 (1.2-3.4)	0.005	2.4 (1.4-4.1)	0.001	2.4 (1.4-4.2)	0.001	0.885
Peripheral	Reference		Reference		Reference		
Shape							
Spherical	Reference		Reference				
Polygonal	1.4 (0.8-2.6)	0.235	0.7 (0.4-1.4)	0.327			
Irregular	4.0 (2.0-8.1)	<0.0001	0.8 (0.4-1.7)	0.512			
Margin							
Smooth	Reference		Reference				
Lobulated	3.8 (2.0-7.0)	<0.0001	1.1 (0.6-2.2)	0.722			
Spiculated	9.0 (4.2-19.4)	<0.0001	1.3 (0.5-3.1)	0.576			
Irregular	5.4 (2.0-14.7)	0.001	0.8 (0.3-2.6)	0.880			
Visibility in retrospect							
Not visible	Reference		Reference		Reference		
Small nodule <15mm^3	0.5 (0.2-1.0)	0.053	4.7 (1.8-12.7)	0.002	4.7 (1.7-12.8)	0.003	1.543

Table 2: Logistic regression analysis of nodule characteristics and volume cutoffs with lung cancer as outcome

*Abbreviations: 95% CI - 95% confidence interval. Missing values were excluded from analyses. Full model equation: logit(p)=-5.31 + Volume 30-<200mm^3*2.818 + Volume >200mm^3*4.825 + Location in right upper lung*0.687 + Central distribution*0.885 + Visibility in retrospect as small nodule <15mm^3*1.543.*

Figure 2 displays the ROC curves of the volume cut-off values, the full model and the model stratified into three risk categories. Discrimination based on volume cut-offs (AUC: 0.80, 95% CI 0.75–0.84) and continuous volume (AUC: 0.82, 95% CI 0.77 to 0.87) was similar. The full model (AUC: 0.85, 95% CI 0.81 to 0.89) provided superior discriminative performance compared with the volume cut-offs alone. The 10-fold cross-validated mean AUC was similar (0.846±0.050). The Hosmer-Lemeshow test was non-significant (P=0.75) suggesting a good overall fit (supplementary figure 1).

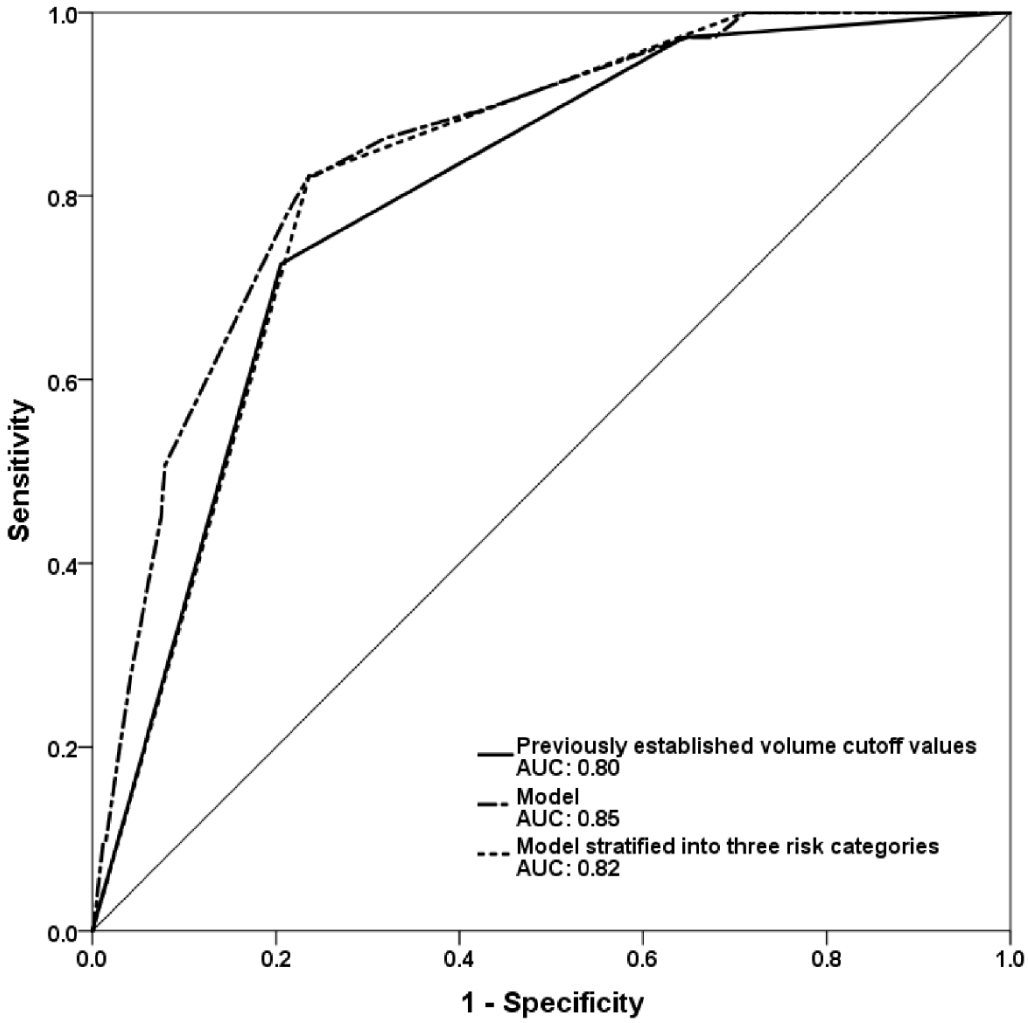

Figure 2: ROC curves of the volume cut-off values, the full model and the full model stratified into three categories for discrimination of lung cancer.
AUC, area under the curve; ROC, receiver operating characteristic curve

The clinical utility of the model in terms of an increased number of true positive predictions without increase in the false-positive rate (net benefit) was assessed over a continuum of potential risk thresholds using decision curve analysis (figure 3). The

model displayed consistent positive and larger net benefit for risk thresholds above 2% (intermediate and high-risk nodule thresholds) when compared with the volume cut-offs alone. Nevertheless, when stratifying nodules into three categories based on model cut-off values for a maximal AUC (AUC: 0.82, 95% CI 0.78 to 0.86), thereby reflecting a three risk-group stratification (low risk, intermediate risk and high risk), there was no significant difference in discriminatory performance compared with the volume cut-offs.

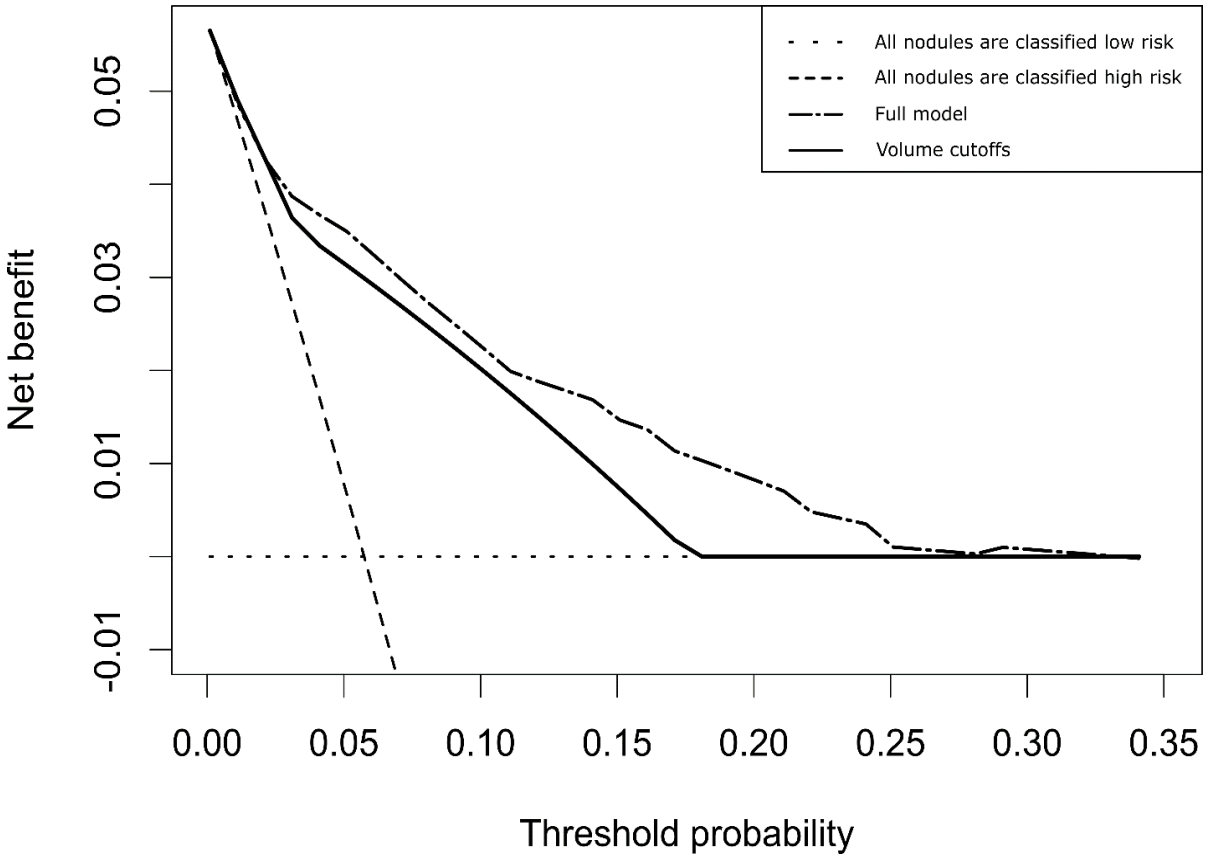

Figure 3 Decision curve analysis of the full model and volume cut-offs alone.
Net benefit: sum of true-positive minus false-positive classifications weighted by the respective risk threshold. For a specific threshold probability, a larger net benefit indicates a greater number of true positive predictions without increase in the rate of false positives. Not using a model would assume that all nodules have the same risk and is illustrated by the two alternatives of either assuming that all nodules are low risk or that all nodules are high risk. This figure illustrates that, when compared with the volume cut-offs, clinical utility of the model is pronounced at higher risk thresholds.

Discussion

This study aimed to evaluate the potential incremental value of morphological and location characteristics to volume-based lung cancer risk stratification of new solid nodules identified after baseline LDCT lung cancer screening. Overall, 1280 new solid nodules detected in 809 participants during the incidence screening rounds of the NELSON trial were included, with 6% (73/1280) being diagnosed as lung cancer.

Studies on new nodules detected in incidence screening rounds of LDCT screening are sparse, and only limited evidence concerning management of these nodules exist.[8,14,32] To our knowledge, this is the first study to investigate the incremental value of morphological and location nodule characteristics to nodule volume cut-offs for lung cancer prediction in new nodules after baseline screening.

We report five central findings. First, at initial detection new solid nodule volume and, therefore, its growth speed was the strongest predictor for malignancy. Second, nodule features traditionally attributed to lung cancer, such as location in the upper lung, central distribution, irregular shape and a lobulated or spiculated margin, were associated with lung cancer in new solid nodules in univariate logistic regression analysis. This is consistent with previous findings, mainly in baseline nodules.[16,19–21] Third, when added to the previously established new solid nodule volume cut-off values (<30 mm^3, 30–<200 mm^3 and ≥200 mm^3),[11,14] only location in the right upper lung and central distribution provided incremental value, while nodule shape and margin did not improve lung cancer discrimination. This contrasts findings in baseline nodules, where aside of location, nodule morphology remained significantly associated with lung cancer when corrected for nodule size.[19–21] This discrepancy may be caused by the augmented predictive information of nodule size in new solid nodules, which developed in a short and known timeframe, as compared with baseline nodules, that could have been present for years before detection. The volume of a baseline nodule primarily represents its current size, whereas the volume of a new nodule more directly translates to its growth rate. This is supported by the observation that only morphological characteristics forfeit their predictive association through addition of nodule volume, while growth independent features remain significant predictors. Next to that, new solid nodules tend to be smaller than baseline nodules at initial detection,[14] which could hamper classification of morphology. Fourth, visibility as very small nodule in retrospect was significantly associated with lung cancer when combined with the volume cut-offs. While this finding could have implications for new nodules ≥30 mm^3 at detection where 22% (6/27) of those visible in retrospect as small nodule were lung cancer as compared with 8% (65/824) of those not visible in retrospect (P=0.02), implications for nodules <30 mm^3 seem redundant considering the respective comparison of <1% (2/228) versus 0% (0/201, p=0.501) being lung cancer. Nodules visible in retrospect likely are persisting nodules that could explain their higher cancer risk when further growing. Fifth, the identified new solid nodule

characteristics did not significantly improve risk stratification by volume when considering a three category (low risk, intermediate risk and high risk) stratification approach such as advocated in current guidelines.[8,11,14] Although some of the selected nodule characteristics provided incremental discriminatory information and clinical utility in decision curve analysis, it was limited compared with the volume cut-offs.

This study has limitations. Nodules that remained <15 mm^3 could not be included as they were below the NELSON trial's detection limit and were not registered by radiologists. Another possible limitation may be observer variation that was not considered. However, single read was only performed by radiologists with at least 6 years of experience in thoracic imaging. Next, only solid nodules were included, with exclusion of part-solid and pure ground glass nodules. Furthermore, nodules without an additional follow-up scan within the NELSON trial were excluded from the analysis to provide the most consistent appreciation of benign and malignant nodules. Because these nodules likely were benign, the proportion of lung cancers may be slightly overrepresented. The overall occurrence and lung cancer probability of new solid nodules within the NELSON trial were reported before.[14]

In new solid nodules detected during incidence screening rounds of LDCT lung cancer screening, morphological and location characteristics only have limited incremental discriminatory value for lung cancer additional to volume cut-offs. Nodule characteristics not influenced by nodule growth, such as location in the right upper lung and a central distribution, can potentially improve volume-based risk stratification, but in a three category (low, intermediate and high risk) stratification approach, this is negligible. Newly detected nodules ≥30 mm^3 and visible as small nodule (<15 mm^3) in retrospect have a high lung cancer probability. Overall, new solid nodule volume and, therefore, speed of growth is the strongest predictor for lung cancer.

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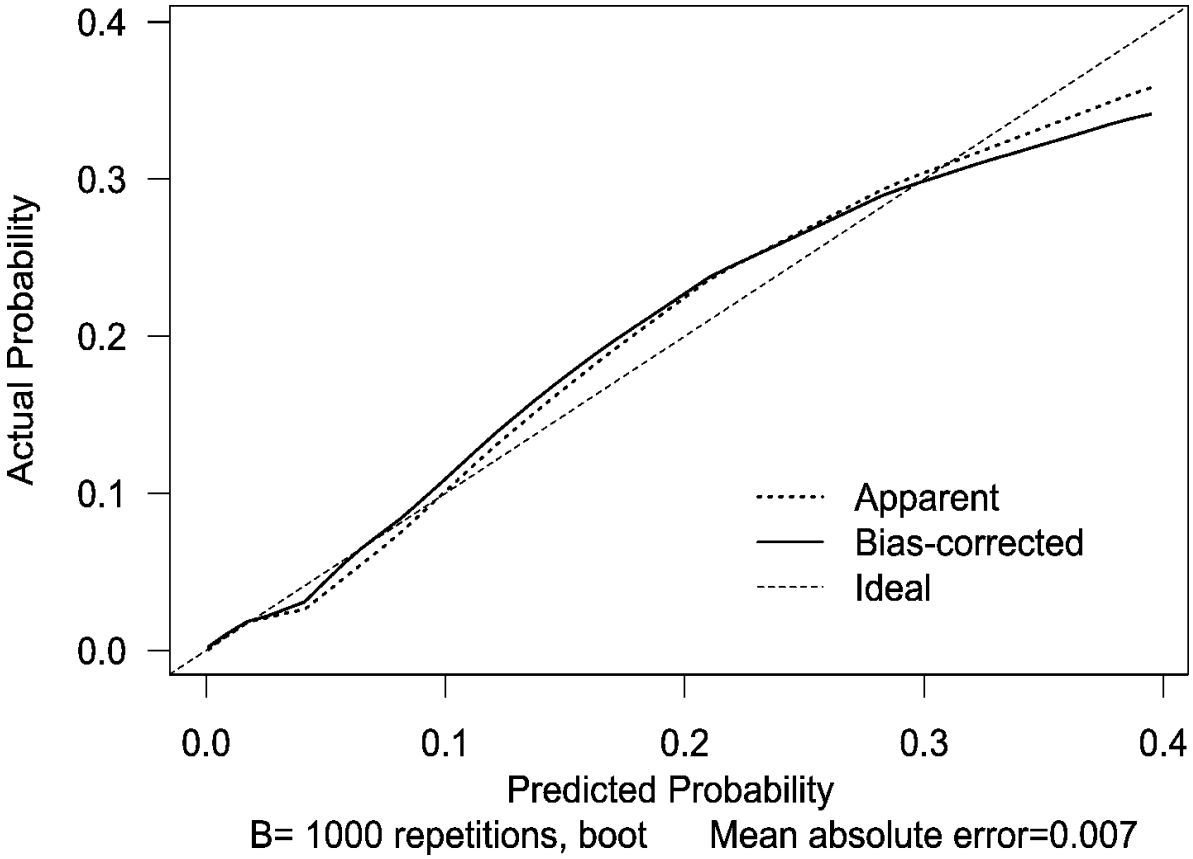
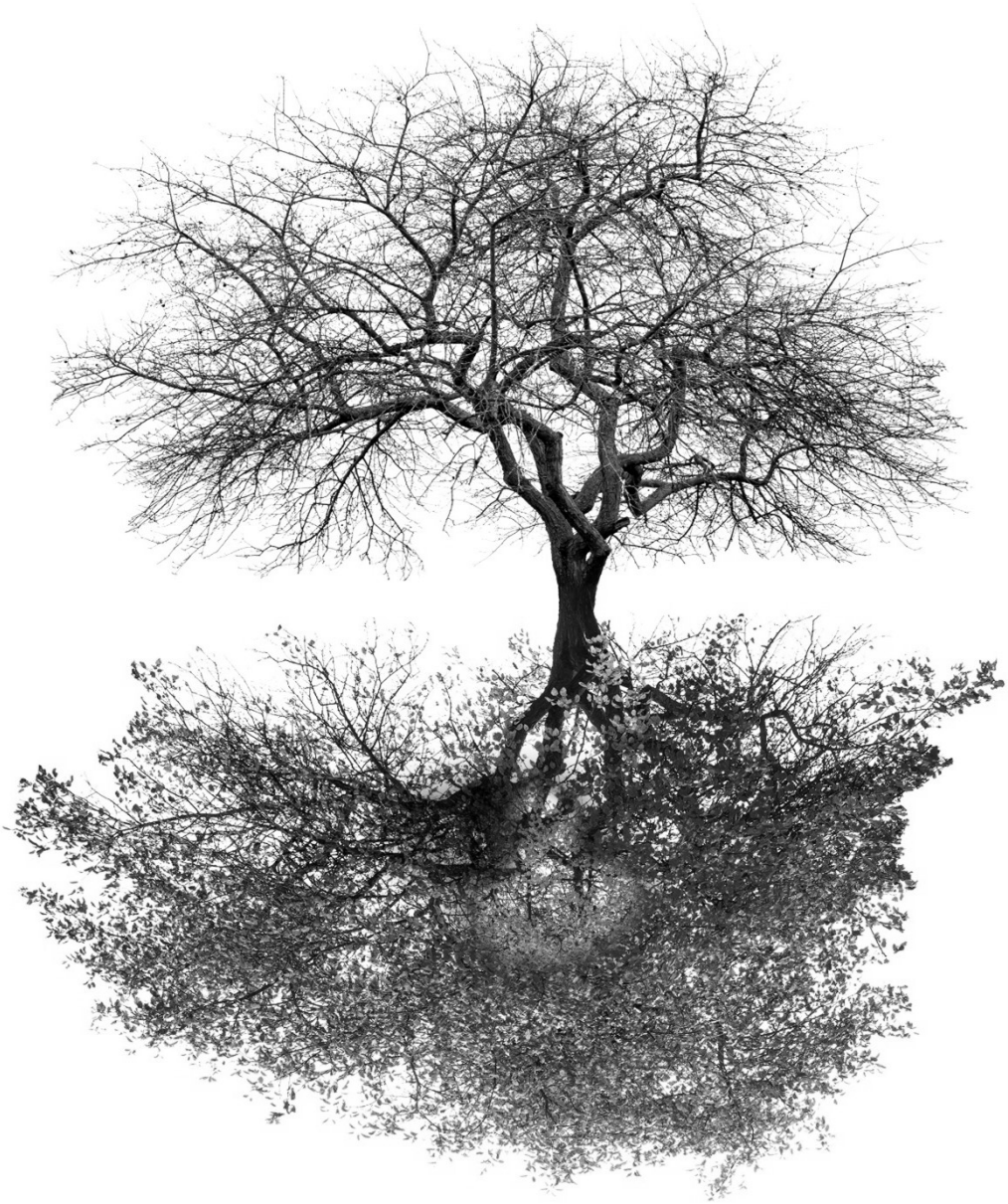
Supplemental Appendix

Characteristics of new solid nodules detected in incidence screening rounds of low-dose CT lung cancer screening: The NELSON study



Supplemental Figure 1: Bootstrap calibration plots of actual probability vs. model predicted probability for lung cancer, with ideal, apparent, and bias-corrected curves



Chapter 7

New subsolid pulmonary nodules in lung cancer screening

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ABSTRACT

Introduction: Low-dose computed tomography (LDCT) lung cancer screening is recommended in the United States. While new solid nodules after baseline screening have a high lung cancer probability at small size and require lower size cutoff values than baseline nodules, there only is limited evidence on management of new subsolid nodules.

Methods: Within the Dutch-Belgian randomized controlled LDCT lung cancer screening trial (NELSON), 7557 participants underwent baseline screening between April 2004 and December 2006**.** Participants with new subsolid nodules detected after the baseline screening round were included.

Results: In the three incidence screening rounds, 60 new subsolid nodules (43 [72%] part-solid, 17 [28%] nonsolid) not visible in retrospect were detected in 51 participants, representing 0.7% (51/7295) of participants with at least one incidence screening. Eventually, 6% (3/51) of participants with a new subsolid nodule were diagnosed with a (pre-)malignancy in such a nodule. All (pre-)malignancies were adenocarcinoma (in situ) and diagnostic work-up (referral 950, 364, and 366 days after first detection respectively) showed favorable staging (stage I). Overall, 67% (33/49) of subsolid nodules with an additional follow-up screening were resolving.

Conclusions: Less than 1% of participants in LDCT lung cancer screening presents with a new subsolid nodule after baseline. Contrary to new solid nodules, data suggest that new subsolid nodules may not require a more aggressive follow-up.

INTRODUCTION

Lung cancer screening is recommended in the US, while European stakeholders are in anticipation of the final results of the randomized-controlled Dutch-Belgian Lung Cancer Screening Trial (NELSON).[1–3] A central challenge in low-dose computed tomography (LDCT) lung cancer screening is the identification of clinically relevant lung cancer, while preventing overdiagnosis and overtreatment.[4] Subsolid nodules are particularly challenging as they carry a relatively high malignancy rate but possess a slow growth rate. Current (clinical) guidelines propose a watchful waiting approach with CT surveillance.[5,6] Nodules found at baseline screening and new nodules thereafter need to be differentiated since they develop within different timeframes. Recently, it was shown that new solid nodules have a high lung cancer risk at small size and require lower size cutoff values than baseline nodules,[7] which was adopted in a European position statement on lung cancer screening.[1] A subsequent analysis of new solid nodules in the National Lung Screening Trial provided similar findings.[8] However, currently there only is limited evidence on management of new subsolid nodules.[9–11] Aim of this study was to assess the occurrence, characteristics and lung cancer probability of subsolid nodules detected in incidence screening rounds of the NELSON trial.

MATERIAL AND METHODS

The NELSON trial (trial registration number, ISRCTN63545820) was authorized by the Dutch Health Care Committee and approved by Ethics Committees of all participating centers in the Netherlands and Belgium. The recruitment process and study design were published before.[12,13] Summarized, eligible patients were adults aged 50–75 years, who had smoked >15 cigarettes per day for >25 years or >10 cigarettes per day for >30 years, and were still smoking or stopped smoking <10 years previously. While the final results of the NELSON trial have not been released yet, most participants are likely Caucasian. Written informed consent was obtained from all participants. Between April 2004 and December 2006, 7,557 participants underwent baseline screening. Three incidence screening rounds took place 1 year, 3 years, and 5.5 years after baseline screening. Details regarding imaging acquisition/analysis and nodule measurements, are provided in the Supplement. Participants with subsolid nodules detected in the three incidence screening rounds and registered as new or previously below the trial's detection limit were assessed.

A nodule was classified as (pre-)malignancy when it was diagnosed as lung cancer during diagnostic workup according to national and international guidelines including histologic assessment. Nodules were classified as benign when either the nodule was benign at histologic examination or diagnostic evaluation had a negative finding. A nodule was also considered benign if it was ruled negative during the participant's last follow-up screening of the NELSON trial and the participant did not present with post-screening lung cancer according to the Dutch and Belgian national cancer registries and medical file review.[14]

Statistical Analysis

Continuous variables are presented as median and inter quartile range (IQR) and categorical variables are presented as frequencies and respective percentages. Confidence intervals of proportions were calculated using the Agresti-Coull method. Nominal variables were analyzed with Fisher's exact test. Statistical significance was considered for $P < 0.05$ and all tests were 2 tailed. Statistical analysis was performed with SPSS version 25.0 (IBM) and R (version 3.3.3).

RESULTS

Within the three incidence rounds of the NELSON trial, 79 new subsolid nodules were detected in 67 participants (0.9% [67/7295] of participants with at least one incidence screening). After exclusion of 16 subsolid nodules that were visible in retrospect according to the NELSON radiologists (31% [5/16] (pre-)malignancies: four adenocarcinoma in situ and one adenocarcinoma stage IA), two new subsolid nodules from one participant with also baseline nodules because the eventual diagnosis (adenocarcinoma in situ) could not be matched unequivocally to a nodule, and one new subsolid nodule because it was a renal cell carcinoma metastasis, a total of 60 new subsolid nodules in 51 participants (0.7% [51/7295] of participants with at least one incidence screening) were included in the final analysis (Figure 1).

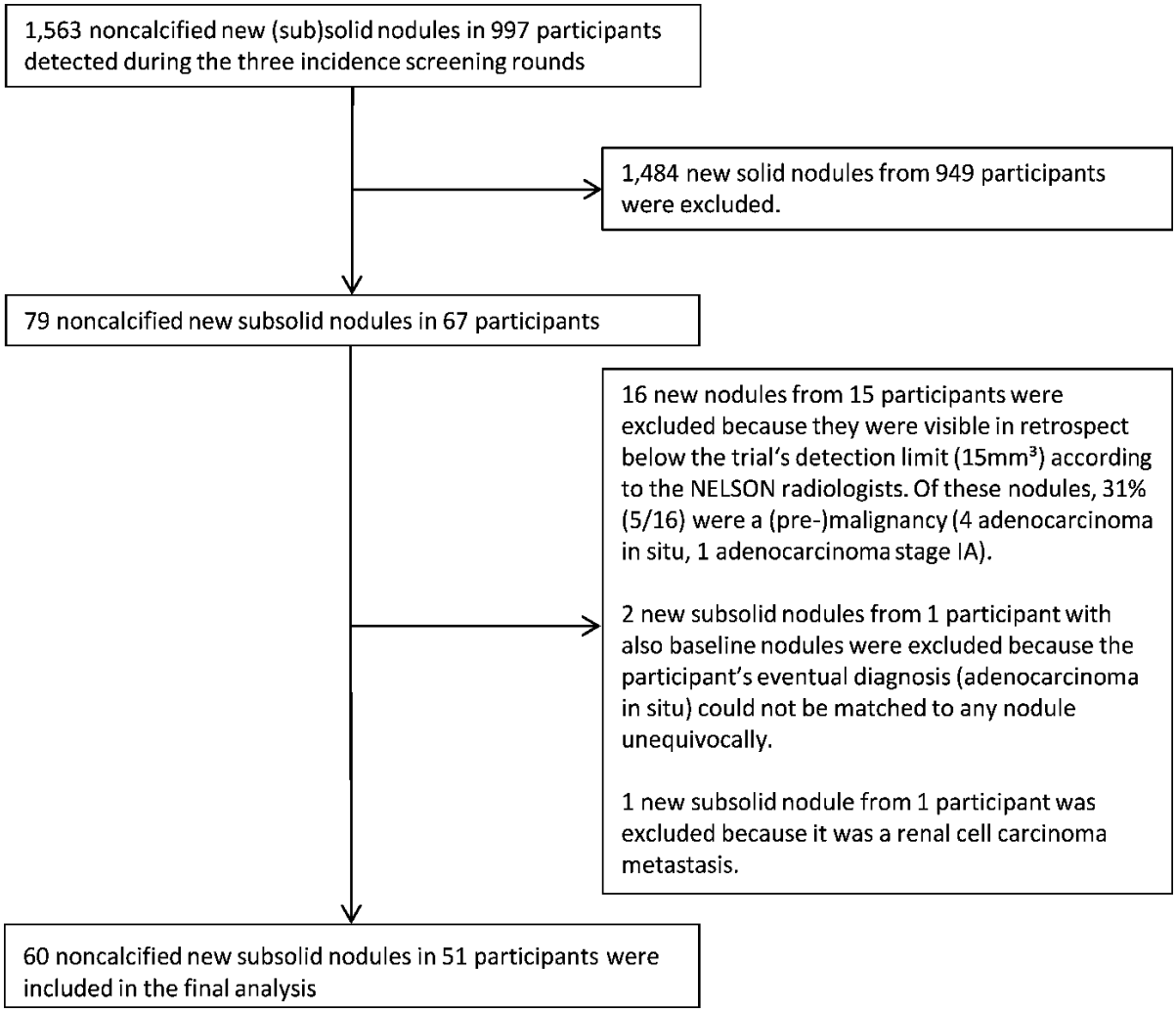

Figure 1: Flowchart of new subsolid nodules in the NELSON trial

Median baseline age of these participants was 59 years (inter quartile range [IQR] 54-63 years), 82% (42/51) were men, and median smoking pack-years at baseline was 39 (IQR 31-49). In total, 25% (15/60) of new subsolid nodules were detected in the second screening round (1 year after baseline), 50% (30/60) in the third screening round (3 years after baseline) and 25% (15/60) in the fourth screening round (5.5 years after baseline). Characteristics of new subsolid nodules and (pre-)malignancy occurrence stratified by subsolid nodule type are presented in Table 1.

	Total subsolid nodules	Part-solid nodules	Nonsolid nodules	P-Value
Total	n=60 (100%)	n=43 (72%)	n=17 (28%)	
Size category				
Nonsolid component <8mm	7/60 (12)	3/43 (7)	4/17 (24)	
Nonsolid component ≥8mm	47/60 (78)	34/43 (79)	13/17 (76)	
Solid component >500mm^3	6/60 (10)	6/43 (14)	0	
Location				0.76
Upper Lung	17/60 (28)	13/43 (30)	4/17 (24)	
Lower Lung	43/60 (72)	30/43 (70)	13/17 (76)	
Distribution*				0.85
Central	10/58 (17)	7/42 (17)	3/16 (19)	
Peripheral	48/58 (83)	35/42 (83)	13/16 (81)	
Margin*				0.54
Smooth	10/56 (18)	6/43 (14)	4/13 (31)	
Lobulated	22/56 (39)	17/43 (40)	5/13 (38)	
Spiculated	3/56 (5)	3/43 (7)	0	
Irregular	21/56 (38)	17/43 (40)	4/13 (31)	
Nodules that received additional screening	49/60 (82)	35/43 (81)	14/17 (82)	
Nonresolving	16/49 (33)	12/35 (34)	4/14 (29)	
Resolving	33/49 (67)	23/35 (66)	10/14 (71)	
(Pre-)malignancies (%, 95% CI)	3/60 (5, 1-14)	1/43 (2, 0-13)	2/17 (10, 2-35)	0.19
(Pre-)malignancies in nonresolving nodules	3/16 (19)	1/12 (10)	2/4 (50)	

Table 1. Characteristics of new subsolid nodules in the three incidence screening rounds
Abbreviations: IQR - Interquartile range.
**Missing values were excluded from analyses.*

Eventually, 6% (3/51) of participants with a new subsolid nodule had a (pre-)malignancy diagnosed in such a nodule (Table 2).

	Nodule 1	Nodule 2	Nodule 3
Nodule type	Part-solid	Non-solid	Non-solid
Mean diameter (mm)	11.7	8.2	10.2
Shape	Non-spherical	Non-spherical	Non-spherical
Margin	Smooth	Smooth	Lobulated
Location	Left upper lobe	Right upper lobe	Right upper lobe
Time until referral (days)	950	366	364
Cancer stage at diagnosis	IA		
Histological type	Invasive non-mucinous adenocarcinoma	Adenocarcinoma in situ	Adenocarcinoma in situ

Table 2. Primary lung cancers detected in new subsolid nodules

After initial detection of a new subsolid nodule, 86% (44/51) of participants received an additional screening in the NELSON trial (1 ended screening and 6 were referred immediately for diagnostic work-up). On first follow-up after initial detection, 33% (16/49) of subsolid nodules had persisted. The median time until first follow-up was 51 days (IQR: 47-87 days). For both nonresolving and resolving nodules the first follow-up primarily took place within 90 days after initial detection (81% and 82%). Of the nonresolving subsolid nodules 75% (12/16) were in the upper lung and 19% (3/16) were (pre-)malignant.

DISCUSSION

This study focused on new subsolid nodules detected in the incidence screening rounds of the NELSON trial. Until now, there are limited data concerning new subsolid nodules detected in LDCT lung cancer screening trials. We report four major findings. First, new subsolid nodules were found in <1% of participants with at least one screening after baseline. Second, only 33% of subsolid nodules with an additional screening after detection persisted until first follow-up. Third, 6% of participants with a new subsolid nodule were diagnosed with a (pre-)malignancy in such a nodule, with 19% of the persistent new subsolid nodules being identified as (pre-)malignant lesion. Fourth, new subsolid (pre-)malignancies were adenocarcinoma (in situ) and diagnostic work-up (referral 950, 364, and 366 days after first detection respectively) showed favorable staging (stage I).

Our study shows that the occurrence of new subsolid nodules is low in a lung cancer screening program and that the lung cancer stage is favorable even with referral after

a year. This is comparable to findings of the I-ELCAP trial, where <1% of participants presented with new part-solid or new non-solid nodules respectively and all lung cancer cases were stage I.[9,10] Similarly, previous prospective studies from Japan indicated the conservative nature of subsolid nodules with all pathologically confirmed tumors being stage I and ≤1% of subsolid nodules being invasive adenocarcinomas.[15,16] Additionally, an analysis of lung cancer manifesting as nonsolid nodule in the National Lung Screening Trial concluded that annual follow-up is appropriate.[17] Furthermore, as also shown in this study, a large proportion of new subsolid nodules resolve until first follow-up, which is comparable to previous reports where 40-70% of subsolid nodules were transient.[18,19] New subsolid nodules that persist may require additional screening or referral for diagnostic work-up with 19% being (pre-)malignant.

Considering the presented data and results of the I-ELCAP trial,[9,10] there is no indication that new subsolid nodules detected after baseline require a more aggressive follow-up than baseline subsolid nodules. This contrasts findings for new solid nodules which have a high lung cancer risk even at small size, necessitating adapted cutoffs.[7]

This study has limitations. Although the NELSON study is the second largest lung cancer screening trial, the number of new subsolid nodules was limited. The precise malignancy rate remains unknown because a part of the nonresolving subsolid nodules were not resected. While these nodules were not diagnosed as interval lung cancer, the final survival rates of the NELSON trial are not yet available.

In conclusion, new subsolid nodules after baseline are rare and often resolve during follow-up. Lung cancer found in new subsolid nodules presents with favorable stage. Considering the existing data, a more aggressive follow-up for new subsolid nodules than for baseline subsolid nodules seems not warranted.

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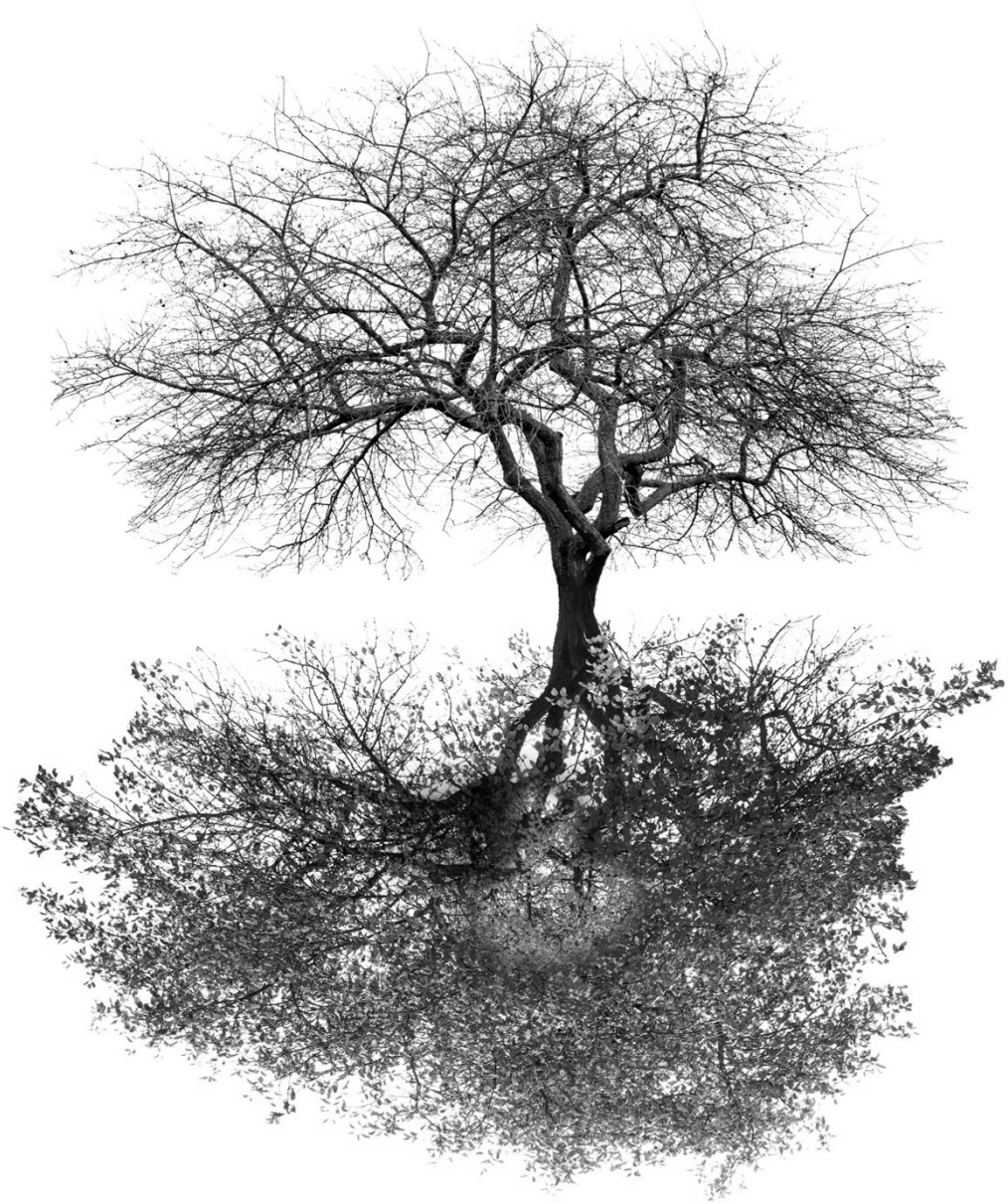
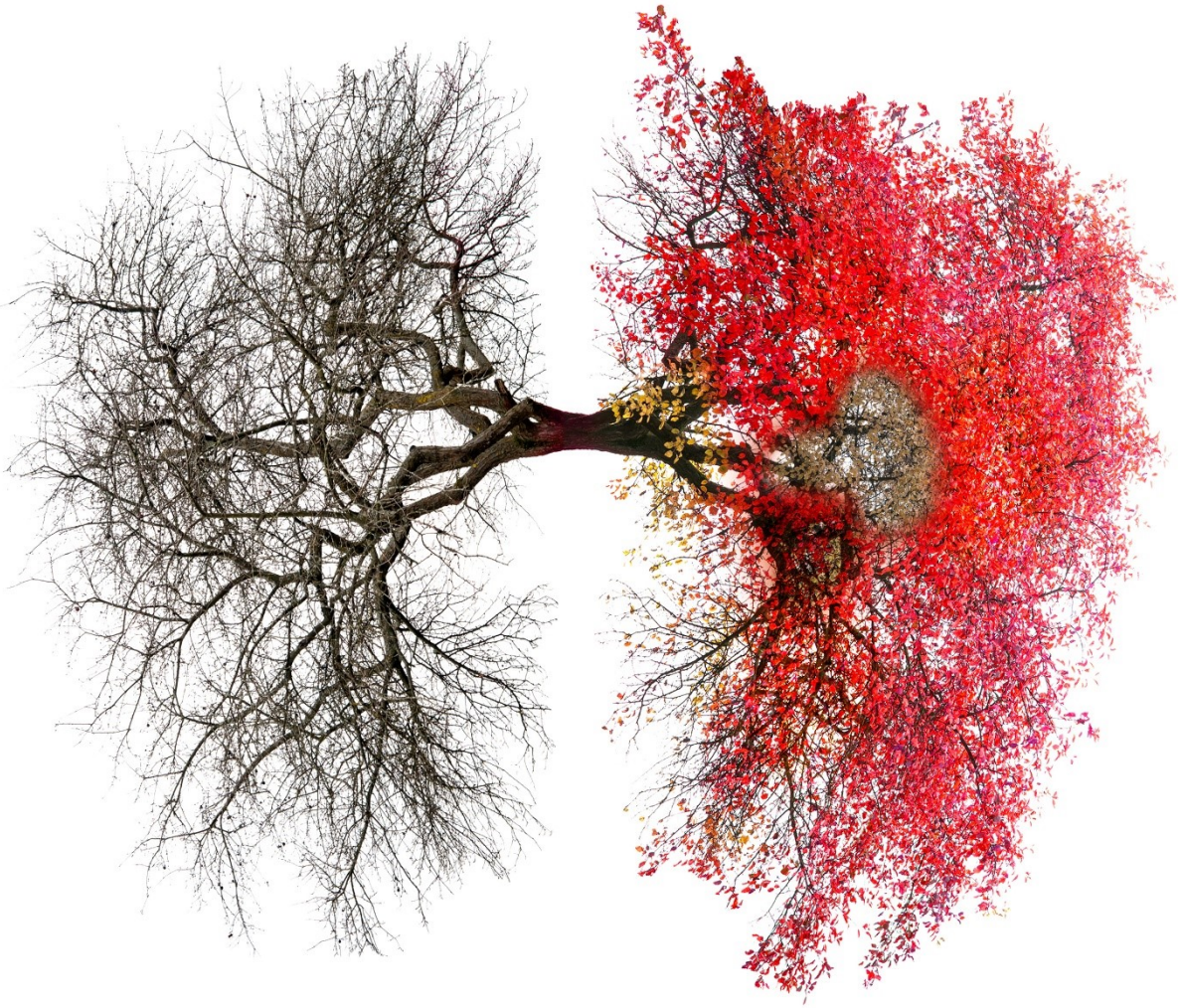


Part III

Number of Nodules and Lung Cancer Probability



Chapter 8

Relationship between nodule count and lung cancer probability in baseline CT lung cancer screening

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ABSTRACT

OBJECTIVES: To explore the relationship between nodule count and lung cancer probability in baseline low-dose CT lung cancer screening.

MATERIALS AND METHODS: Included were participants from the NELSON trial with at least one baseline nodule (3392 participants [45% of screen-group], 7258 nodules). We determined nodule count per participant. Malignancy was confirmed by histology. Nodules not diagnosed as screen-detected or interval cancer until the end of the fourth screening round were regarded as benign. We compared lung cancer probability per nodule count category.

RESULTS: 1746 (51.5%) participants had one nodule, 800 (23.6%) had two nodules, 354 (10.4%) had three nodules, 191 (5.6%) had four nodules, and 301 (8.9%) had>4 nodules. Lung cancer in a baseline nodule was diagnosed in 134 participants (139 cancers; 4.0%). Median nodule count in participants with only benign nodules was 1 (Inter-quartile range [IQR]: 1-2), and 2 (IQR 1-3) in participants with lung cancer (p=NS). At baseline, malignancy was detected mostly in the largest nodule (64/66 cancers). Lung cancer probability was 62/1746 (3.6%) in case a participant had one nodule, 33/800 (4.1%) for two nodules, 17/354 (4.8%) for three nodules, 12/191 (6.3%) for four nodules and 10/301 (3.3%) for>4 nodules (p=NS).

CONCLUSION: In baseline lung cancer CT screening, half of participants with lung nodules have more than one nodule. Lung cancer probability does not significantly change with the number of nodules. Baseline nodule count will not help to differentiate between benign and malignant nodules. Each nodule found in lung cancer screening should be assessed separately independent of the presence of other nodules.

Introduction

In 2011, the National Lung Screening Trial (NLST) reported a 15–20% reduction in lung cancer mortality among individuals screened by annual low-dose CT, if compared to participants screened by annual chest X-ray [1]. Following the publication of this positive result, adapted guidelines were published, all recommending lung cancer screening in a high-risk population [2–5]. A remaining problem in lung cancer screening, however, is the high rate of false-positive screen results.

In CT lung cancer screening trials, about half of screened participants have pulmonary nodules, the overwhelming majority being benign [1,6,7]. A key issue in lung cancer screening is to differentiate benign and malignant nodules at an early stage. Several radiological features, such as size, growth rate, morphology, and location are associated with an increased lung cancer probability and may help radiologists in adequately identifying a high-risk baseline nodule [8,9].

A commonly overlooked aspect is the number of nodules per screenee (nodule count) at the time of nodule detection. Generally, nodule management in lung cancer screening is based on the largest or most suspicious nodule, but often more than one nodule is present. While only limited data concerning the impact of nodule count on lung cancer probability is available, one study indicated a negative linear relationship between nodule count and lung cancer probability and incorporated it in a risk calculator for nodules detected at baseline screening [10].

However, in a preliminary, limited analysis on multinodularity and lung cancer probability for nodules detected in the first and second screening round of the Dutch-Belgian Randomized Lung Cancer Screening Trial (acronym NELSON), the relationship between nodule count and lung cancer probability in participants was found to be ambiguous, with varying lung cancer probabilities as nodule count increased [7]. The purpose of this study was to explore in-depth the relationship between nodule count and lung cancer probability in the baseline round of the NELSON trial.

Materials and methods

NELSON trial and study participants

The NELSON trial was designed to investigate whether low-dose spiral CT screening will decrease 10-year lung cancer mortality by at least 25% in high-risk (ex-) smokers.

The Dutch Minister of Health and the ethics board of each participating center approved the NELSON trial. All participants gave written informed consent. The design of the NELSON trial, including participant selection and lung nodule management has been published [11,12]. In brief, 15,792 current and former smokers [13], aged 50–75 years, who smoked > 15 cigarettes daily for over 25 years or > 10 cigarettes daily for over 30 years were included. Participants were randomized 1:1 to usual care without screening or screening. Between April 2004 and December 2006, 7557 participants underwent baseline screening. Baseline screening was performed in year 1, and incident screening rounds took place in year 2 (second round), year 4 (third round), and year 6.5 (fourth round). For this retrospective analysis, we included all participants with non-calcified nodules detected at baseline. We included all nonsolid, part-solid and solid nodules with volume ≥ 15 mm3 and/or sub-solid diameter ≥ 4 mm (study detection limits).

Lung cancer screening

CT scan protocol, reading and data set Participants were invited to one of four screening sites each using a 16-multidetector CT scanner (three Sensation-16 systems, Siemens Medical Solutions, Forchheim, Germany and one Brilliance 16P system, Philips Medical Systems, Cleveland, OH, USA). A non-contrast low-dose CT scan of the entire chest was obtained in a cranio-caudal direction in one breath-hold (about 12 s in spiral mode with 16 × 0.75 mm collimation and pitch 1.3). Typical technical parameters for the low-dose setting depended on body weight (< 50 kg, 50–80 kg and > 80 kg): 80–90 kVp, 120 kVp and 140 kVp respectively [11]. Image data sets with isotropic voxels were available, allowing analyses with software for semi-automated volume measurements (Syngo LungCARE, Siemens Healthcare, Erlangen, Germany). All images were read by two independent radiologists with experience in chest CT reading ranging between 1 and 20 years, and in case of discrepancy a third, expert reader made the final decision [11,14]. Radiologists could overrule a protocol-based screening result (done for 6% of participants at the baseline screening round) and manually adjust the volume measurement in case of inappropriate segmentation [14]. Nodule management was based on size, density and growth rate of the largest nodule. The nodule size criteria were published before [11]. In short, NODCAT 2 comprised solid nodules with volume 15–50 mm3 and subsolid nodules with diameter 4–8 mm, and led to a negative screen result (invitation for

regular next screening round). NODCAT 3 were solid nodules with volume 50–500 mm3 and subsolid nodules ≥ 8 mm. NODCAT 4 nodules were defined as potentially malignant (solid, > 500 mm3 , positive screen result), and required immediate referral to the pulmonologist for work-up. NODCAT 3 nodules were assigned an indeterminate test result, requiring a repeat scan after 3–4 months to assess nodule growth. Growth was defined as change in volume of > 25% and volume doubling-time was calculated as described previously [11,15]. Screenees having a nodule with volume doubling time < 400 days (fast growing, positive screen result) were referred to a pulmonologist for work-up.

Nodule characteristics

Both readers reported information regarding nodule volume, location, distance to costal pleura and margin. Nodule location was defined as upper lobe (middle, left or right upper lobe) or lower lobe (left or right lower lobe). In case of distance to costal pleura less than one-third of the total distance of hilum-costal pleura, nodules were considered to be peripheral, and with more than one-third of the total distance, nodules were considered to be non-peripheral. Nodule margin was classified as smooth, lobulated, spiculated or irregular [16].

Nodule count

Nodule count was defined as the number of non-calcified lung nodules present in the baseline screening round. We compared nodule count at baseline for participants with only benign nodules and participants with lung cancer. Five categories based on nodule count were defined: 1 nodule, 2 nodules, 3 nodules, 4 nodules and > 4 nodules. Histology was the reference for diagnosis. In case a nodule was not diagnosed as screen-detected lung cancer or interval cancer until the end of the fourth screening round, the nodule was regarded as benign.

Statistical analysis

Descriptive statistics were reported as numbers and percentages. We tested data distribution with normality plots. Normally distributed variables were described by mean and 95% confidence interval (95%- CI), while non-normally distributed variables were described by median and inter-quartile range (IQR). We assessed the relationship of participant age and smoked pack-years with nodule count by using

Spearman's rank correlation coefficient. We derived lung cancer probability per screenee and per nodule for categories based on number of baseline nodules, by dividing the number of lung cancer cases per category by number of screenees and number of nodules, respectively. We tested the relationship between the presence of lung cancer and the number of baseline nodules by using chi-square. We used SPSS Statistics version 22 (IBM, Armonk, NY) for all analyses, and considered a p-value of < 0.05 as statistically significant.

Results

Characteristics of study population

In this study, we included 3392 participants with 7258 non-calcified baseline nodules (45% of all screen-group participants). Median participant age was 58 years (IQR 55–63 years); 84.4% (2863/3392) were male (Table 1). In total, 1746 participants (51.5%) had one nodule, 800 (23.6%) had two nodules, 354 (10.4%) had three nodules, 191 (5.6%) had four nodules, and 301 (8.9%) had five or more nodules. Fig. 1 shows the distribution of nodule count per participant. The percentage of screenees with actionable nodules (NODCAT 3 or 4; short-term follow-up or referral) increased linearly with the number of baseline nodules, from 36.4% to 90.0% (Table 1). Spearman's correlation coefficient showed slightly more nodules by increasing age (correlation coefficient 0.044; $p = 0.01$). No difference was found in number of nodules by smoked pack-years (correlation coefficient 0.026; $p = 0.13$).

		All participants N=3,392	1 Nodule N=1,746	2 Nodules N=800	3 Nodules N=354	4 Nodules N=191	>4 Nodules N=301
Age	Median	58	58	59	59	59	59
	IQR	55-63	54-63	55-63	55-63	55-64	55-63
Pack Years	Median	38.0	37.9	38.7	37.9	38.7	37.9
	IQR	29.7-49.5	29.7-49.5	29.7-49.5	29.7-49.5	31.2-53.2	29.7-49.5
Gender	Male N (%)	2,863 (84.4)	1,455 (83.3)	674 (84.3)	298 (84.2)	169 (88.5)	267 (88.7)
NODCAT_max[a]	2, N (%)	1,616 (47.6)	1,109 (63.5)	333 (41.6)	106 (29.9)	38 (19.9)	30 (10)
	3, N (%)	1,588 (46.8)	570 (32.6)	416 (52.0)	219 (61.9)	134 (70.2)	249 (82.7)
	4, N (%)	188 (5.5)	67 (3.8)	51 (6.4)	29 (8.2)	19 (9.9)	22 (7.3)

Table 1: Characteristics of participants with at least one pulmonary nodule at baseline screening round

[a] Largest nodule at baseline screening. A NODCAT 2 nodule is solid nodules with volume 15-50 mm³ or sub-solid with diameter 4-8 mm, a NODCAT 3 nodule is solid with volume 50-500 mm³, or sub-solid ≥8 mm, and a NODCAT 4 nodule is solid >500 mm³.

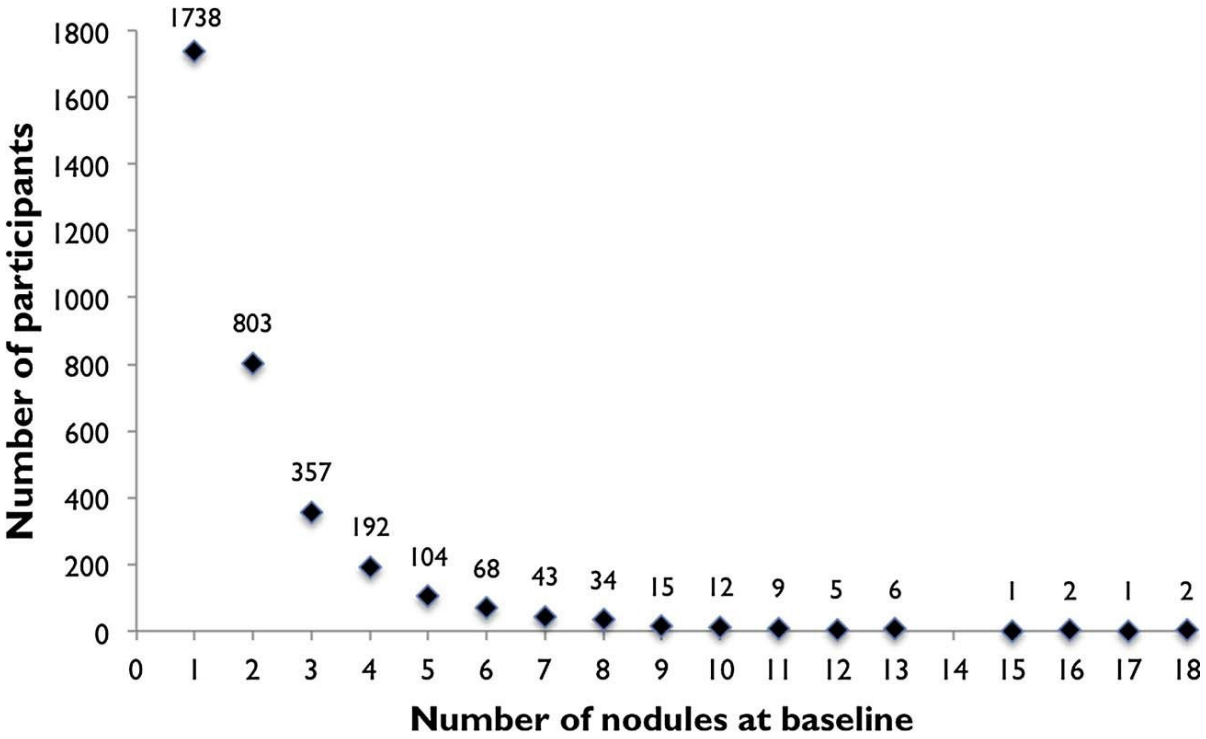

Figure 1: Distribution of nodule count in 3389 participants at baseline lung cancer screening

Description of cancers in study population

During four screening rounds, 139 baseline nodules in 134 participants were proven to be lung cancer. Simultaneous double tumours were found in five participants. Of the 139 cancers, 70 were diagnosed to be malignant immediately after the baseline round (66 screenees). At baseline, lung cancer was histologically confirmed in the largest nodule in 64/66 (97.0%) screenees (double tumours counted once), and in the second largest detected nodule in 2/66 (3.0%) cases. In later rounds, 49/56 (87.5%) screen-detected lung cancers and 10/12 (83.3%) interval cancers were found in baseline nodules that were the largest at the baseline CT. On population basis, median nodule count was 1 (IQR 1–2) in participants with only benign nodules, and 2 (IQR 1–3) in participants with lung cancer. Range of nodule count was equal for participants with only benign nodules and participants with lung cancer (1–18 nodules).

Nodule characteristics

Baseline nodules most often were located in the lower lobes, in the periphery of the lung, and had a smooth shape. Compared to benign baseline nodules, malignant

nodules were larger and more often subsolid, had more often a non-smooth margin, and were more often located in the upper lobes of the lung. Nodule characteristics per nodule count are shown in Table 2.

Lung cancer probability: participant-based analysis

In 62 of 1746 participants with one baseline nodule (3.6%; 95% CI, 2.8-4.6%), the solitary nodule was lung cancer. Of 800 participants with two lung nodules, 33 (4.1%; 95% CI, 2.9-5.8%) were diagnosed with lung cancer in one of these nodules. In 17 of 354 participants with three nodules (4.8%; 95% CI, 2.9-7.7%), 12 of 191 participants with four nodules (6.3%; 95% CI, 3.4-11.0%), and ten of 301 participants with at least five nodules (3.3%; 95% CI, 1.7-6.2%), lung cancer was diagnosed (Table 3). Lung cancer probability did not differ significantly for the different nodule count categories ($p = 0.34$).

Of the 12 participants with a baseline nodule diagnosed as interval cancer, three participants had a single baseline nodule, five had two nodules at baseline, two had three baseline nodules, one had four and one had > 4 nodules at baseline.

Lung cancer probability: nodule-based analysis

Lung cancer probability per nodule was 3.6% in case of one nodule, 2.1% in case of two nodules, 1.8% in case of three nodules, 1.7% in case of four nodules and 0.7% in case of screenees with more than four nodules.

Table 4 shows an increasing lung cancer risk in increasing nodule categories (overall; NODCAT 2 0.3%, NODCAT 3 2.5% and NODCAT 4 30.1%). There was no difference in lung cancer probability for a NODCAT 2 nodule found in screenees with only one nodule or screenees with a higher nodule count. For actionable nodules (> 50 mm^3; NODCAT 3 or 4), the risk of malignancy in a particular nodule decreased in case a nodule was found in screenees with four or more nodules per screenee, compared to actionable nodules found in screenees with only one nodule ($p < 0.001$ for NODCAT 3 and $p < 0.05$ for NODCAT 4 nodules).

		1 Nodule	2 Nodules	3 Nodules	4 Nodules	>4 Nodules	*Benign*	*Malignant*	*P-value*
Volume (mm^3)[a]	Median	36.9	38.3	38.3	38.6	38.9	*37.7*	*328.6*	*<0.001*
	IQR	23.8-69.0	24.1-70.3	25.1-70.1	24.9-71.6	24.6-67.5	*24.2-67.3*	*112.7-1130.5*	
NodCat	2	959 (64.0)	972 (62.0)	707 (63.5)	476 (62.3)	1,444 (62.4)	*4545 (63.8)*	*13 (9.4)*	*<0.001*
	3	484 (32.3)	537 (34.2)	374 (33.6)	263 (34.4)	834 (36.0)	*2,430 (34.1)*	*64 (46.0)*	
	4	55 (3.7)	60 (3.8)	32 (2.9)	25 (3.3)	36 (1.6)	*144 (2.0)*	*62 (44.6)*	
Nodule Type[b]	Solid	1,439 (96.8)	1,504 (96.5)	1,074 (96.7)	744 (97.4)	2,277 (98.6)	*6,915 (97.5)*	*123 (88.5)*	*<0.001*
	Part-solid	15 (1.0)	27 (1.7)	18 (1.6)	8 (1.0)	11 (0.5)	*72 (1.0)*	*7 (5.0)*	
	Nonsolid	33 (2.2)	28 (1.8)	19 (1.7)	11 (1.4)	21 (0.9)	*103 (1.5)*	*9 (6.5)*	
Location[c,d]	Upper Lobe	569 (38.6)	620 (40,0)	381 (34.9)	276 (34.9)	760 (34.2)	*2,517 (36.2)*	*89 (64.0)*	*<0.001*
	Lower lobe	906 (61.4)	929 (60,0)	712 (65.1)	472 (63.1)	1,465 (65.8)	*4,434 (63.8)*	*50 (36.0)*	
	Peripheral	1,204 (81.6)	1,252 (80.7)	923 (83.2)	623 (81.9)	1,983 (86.1)	*5,872 (83.1)*	*113 (81.9)*	*0.73*
	Non-peripheral	271 (18.4)	300 (19.3)	186 (16.8)	138 (18.1)	321 (13.9)	*1,191 (16.9)*	*25 (18.1)*	
Shape[e]	Non-smooth	89 (6.9)	108 (7.8)	67 (6.9)	30 (4.8)	65 (3.1)	*299 (4.9)*	*60 (45.5)*	*<0.001*
	Smooth	1,206 (93.1)	1,276 (92.2)	903 (93.1)	594 (95.2)	1,920 (96.7)	*5,827 (95.1)*	*72 (54.5)*	

Table 2: Nodule characteristics detected at baseline screening round.

Unless otherwise indicated, data are numbers of nodules, with percentages in parenthesis. Abbrevations: IQR – Interquartile range.

[a] In 193/7258 (2.7%) no volume measurement was possible, for instance in sub-solid nodules.

[b] In 29/7258 (0.4%) nodule type was not specified, mostly due to very small nodule size (<50 mm^3).

[c,d] In 225/7258 (3.1%) location was not specified (168/7258 (2.3%) peripheral versus non peripheral and 57/7258 (0.8%) upper versus lower lobe).

[e] In 1000/7258 (13.8%) nodule shape was not specified, mostly due to very small nodule size (<50 mm^3).

Nodule Count	Participants	Total Cancer	Lung cancer probability	95% CI	Baseline Cancer	Lung cancer probability Baseline	95% CI Baseline	Cancer in later round*	Lung cancer probability Incidence round	95% CI Incidence round
1 Nodule	1,746	62	3.6%	2.8-4.6%	30	1.7%	1.2-2.5%	32	1.8%	1.3-2.6%
2 Nodules	800	33	4.1%	2.9-5.8%	17	2.1%	1.3-3.5%	16	2.0%	1.2-3.3%
3 Nodules	354	17	4.8 %	2.9-7.7%	6	1.7%	0.7-3.8%	11	3.1%	1.6-5.7%
4 Nodules	191	12	6.3%	3.4-11.0%	7	4.2%	2.0-8.4%	5	2.6%	1.0-6.3%
>4 Nodules	301	10	3.3%	1.7-6.2%	6	2.0%	0.8-4.5%	4	1.3%	0.4-3.6%
Total	*3,392*	*134*	*4.1%*	*3.4; 4.8%*	*66*	*2.0%*	*1.5; 2.5%*	*68*	*2.0%*	*1.6; 2.6%*

Table 3: Lung cancer probability with 95% confidence intervals on participant basis: cancer detection at baseline versus at later screening rounds

Note - Data are numbers of participants, with percentages in parenthesis; Abbreviations: 95% CI - 95% confidence interval. lung cancer diagnosed in a nodule already present at baseline*

Baseline NODCAT	NODCAT 2 Nodules		NODCAT 3 Nodules		NODCAT 4 Nodules	
Cancer	Yes	No	Yes	No	Yes	No
Overall cancer	*13 (0.3)*	*4,545 (99.7)*	*64 (2.6)*	*2,431 (97.4)*	*62 (30.1)*	*144 (69.9)*
Nodule count 1	6 (0.5)	1,102 (99.5)	29 (5,1)	543 (94,9)	27 (40.9)	39 (59.1)
Nodule count 2	4 (0.4)	988 (99.6)	16 (2.9)	536 (97.1)	15 (26.8)	41 (73.2)
Nodule count 3	3 (0.4)	682 (99.6)	9 (2.6)	334 (97.4)	7 (20.6)	27 (79.4)
Nodule count 4	0 (0)	471 (100)	7 (2.6)	265 (97.4)	6 (28.6)	15 (71.4)
Nodule count > 4	0 (0)	1,302 (100)	3 (0.4)	753 (99.6)	7 (24.1)	22 (75.9)

Table 4. Lung cancer probability by nodule count for NODCAT* 2-4 nodules

**A NODCAT 2 nodule is solid nodules with volume 15-50 mm³ or sub-solid with diameter 4-8 mm, a NODCAT 3 nodule is solid with volume 50-500 mm³, or sub-solid ≥8 mm, and a NODCAT 4 nodule is solid >500 mm³*

Discussion

With the use of multi-detector low dose CT scanners (very) small lung nodules can be detected, the minority being malignant. Whether the number of lung nodules (nodule count) plays a role in the determination of lung cancer probability still remains largely unknown. This study shows that at baseline CT lung cancer screening, nearly half of screening participants with lung nodules have more than one lung nodule (1746/3392 [51.5%]), representing about one-fourth of all screenees. We found no statistically significant relationship between nodule count and lung cancer probability in participants with baseline nodules. We observed a non-significant trend whereby lung cancer probability increased as a function of nodule count, with a peak in lung cancer probability in subjects with four baseline nodules (6.3%). However, this non-significant increasing trend did not continue. The implications of these findings partly differ from previous observations by McWilliams et al., where nodule count was incorporated in a model for the prediction of malignancy in pulmonary nodules [10]. In their risk calculator, they found a linear reduction of a baseline nodule's lung cancer probability with an increased number of pulmonary nodules per screenee.

In our subgroup of the NELSON study containing all participants with non-calcified baseline nodules, we found lung cancer in a baseline nodule in 134/3392 (4.0%) participants, up to six years after baseline (information regarding new nodules was published elsewhere [17]). In the PanCan study, the overall rate of malignancy was 5.5%. In comparison to the findings of McWilliams et al. [10], we found a much lower mean nodule count per screened participant. The subjects with benign nodules in the PanCan study had a mean of 6.2 nodules, compared to 2.1 nodules (median 1 nodule) in our study. In the PanCan study, subjects with lung cancer had a mean of 4.8 nodules, in contrast to our findings of 2.3 nodules on average (median 2 nodules). Differences may be explained by differences in inclusion criteria for screenees. The NELSON study recruited participants aged 50–75 years without a history of lung cancer, who smoked > 15 pack-years. The PanCan study used a different approach for recruiting participants, namely via a risk-prediction model [18]. Participants with an estimated risk of developing lung cancer in the next 3 years of ≥ 2% were included. Geographical differences in pulmonary nodule nature (i.e. prevalence of fungus infestations [19]) may have influenced the number of nodules in these studies on two different continents as well.

In 64/66 (97.0%) of participants with lung cancer detected at baseline, malignancy was detected in the nodule with the largest volume. This contrasts with the results by McWilliams et al. [10], who showed that in one-fifth of the participants, the largest nodule was not the one that turned out to be malignant at baseline or follow-up. This discrepancy might be explained by the use of semi-automated, volumetric measurement in our study, while manual, two-dimensional diameter measurements were performed in the PanCan study. Previously, it has been shown that nodule measurements are more accurate with volumetric techniques compared to diameter techniques [20–22]. Possibly, diameter measurements cannot identify the largest nodule as good as volumetry.

The American College of Radiology's Lung Imaging Reporting and Data System (Lung-RADS) proposed to classify screening CTs by the nodule with highest malignant risk (usually the largest nodule) [23]. Our results confirm this policy. Each nodule found in lung cancer screening subjects should be assessed separately whereby the largest nodule has the highest probability to be malignant. While reporting and measuring all lung nodules might be time consuming, it is important to lung cancer screening for two reasons. First, new nodules are regularly found after baseline screening and were shown to carry a higher lung cancer probability than do baseline nodules even at smaller size [24]. To ensure the appropriate detection of new nodules, previously present nodules need to be well documented. Secondly, after initial detection a nodule's risk-stratification relies on growth assessment which is based on the size difference between two scans and therefore the previous measurements [7,25].

We found that the more nodules per screenee, the greater the likelihood that the largest nodule was classified as indeterminate (NODCAT 3, see Table 1). Indeterminate pulmonary nodules led to an extra follow-up CT examination after 3 months. Therefore, the more nodules per screenee, the more follow-up scans were made to assess growth.

Higher age and number of smoked pack-years are associated with an increased risk of developing lung cancer [10]. In our analysis, higher age at baseline was correlated with a slightly increased risk of having more pulmonary nodules. In contrast, no relationship was found between nodule count at baseline and number of smoked pack-years.

We included all non-calcified nodules, and did not differentiate between solid, part-solid and pure nonsolid nodules. More detailed research on the influence of multiple

nodules from different subtypes (solid, sub-solid) on lung cancer probability is recommended. Furthermore, external validation of the nodule count and lung cancer probability in high-risk screening participants needs to be performed to confirm our findings.

Conclusion

At baseline CT lung cancer screening, nearly half of screened participants with lung nodules have more than one lung nodule, representing a quarter of all screenees. Lung cancer probability did not significantly change with number of nodules, therefore baseline nodule count proved to be not useful for prediction of malignancy. Each nodule found in lung cancer screening subjects should be assessed separately independent of the presence of other nodules.

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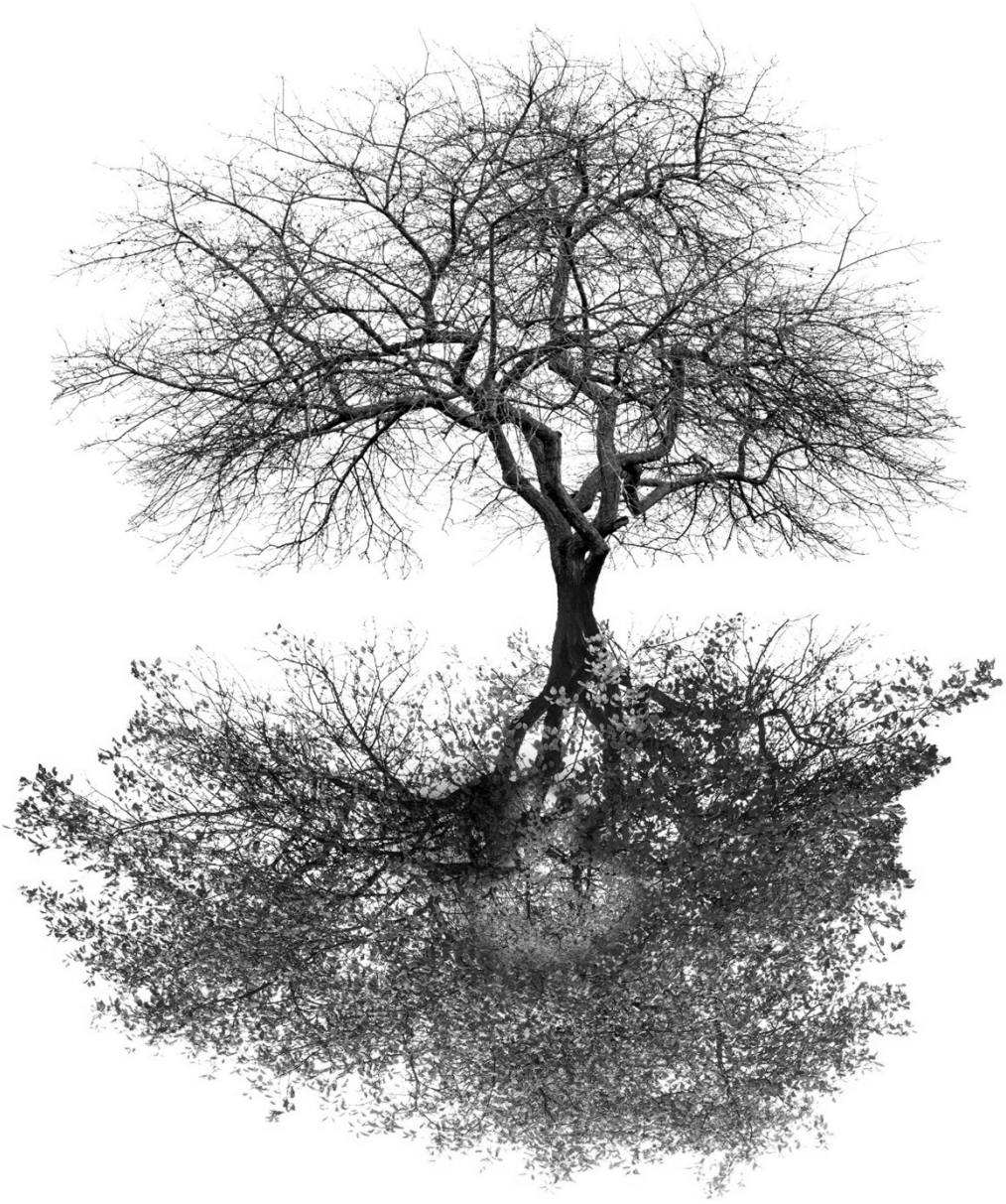

Chapter 9

Relationship between the number of new nodules and lung cancer probability in incidence screening rounds of CT lung cancer screening

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ABSTRACT

Background: New nodules are regularly found after the baseline round of low-dose computed tomography (LDCT) lung cancer screening. The relationship between a participant's number of new nodules and lung cancer probability is unknown.

Methods: Participants of the ongoing Dutch-Belgian Randomized Lung Cancer Screening (NELSON) Trial with (sub)solid nodules detected after baseline and registered as new by the NELSON radiologists were included. The correlation between a participant's new nodule count and the largest new nodule size was assessed using Spearman's rank correlation. To evaluate the new nodule count as predictor for new nodule lung cancer together with largest new nodule size, a multivariable logistic regression analysis was performed.

Results: In total, 705 participants with 964 new nodules were included. In 48% (336/705) of participants no nodule had been found previously during baseline screening and in 22% (154/705) of participants >1 new nodule was detected (range 1-12 new nodules). Eventually, 9% (65/705) of the participants had lung cancer in a new nodule. In 100% (65/65) of participants with new nodule lung cancer, the lung cancer was the largest or only new nodule at initial detection. The new nodule lung cancer probability did not differ significantly between participants with 1 (10% [56/551], 95%CI 8-13%) or >1 new nodule (6% [9/154], 95%CI 3-11%, P=0.116). An increased number of new nodules positively correlated with a participant's largest nodule size (P<0.001, Spearman's rho 0.177). When adjusted for largest new nodule size, the new nodule count had a significant negative association with lung cancer (odds ratio 0.59, 0.37-0.95, P=0.03).

Conclusion: A participant's new nodule count alone only has limited association with lung cancer. However, a higher new nodule count correlates with an increased largest new nodule size, while the lung cancer probability remains equivalent, and may improve lung cancer risk prediction by size only.

Introduction

Lung cancer screening using low-dose computed tomography (LDCT) is currently recommended by US guidelines for high-risk individuals,[1–3] after the National Lung Screening Trial reported a 20% reduced lung cancer mortality for LDCT compared to chest radiography screening.[4] Lung nodules are common findings in LDCT lung cancer screening. European and American trials with no or very low detection limits reported a noncalcified lung nodule prevalence in 41-51% of participants at baseline screening.[5–9] Since most detected nodules are benign, the effective identification of potentially malignant nodules is central to current lung cancer screening programs. While nodule management is mainly based on size and growth,[10,11] other nodule characteristics, such as nodule morphology or nodule location, have traditionally been associated with an increased probability for lung cancer. [10–13] Furthermore, patient characteristics such as age or smoking pack-years play a crucial role in identifying high-risk individuals eligible for screening.[8,12,14]

However, within a lung cancer screening program, but also in regular clinical practice, individuals may be diagnosed with several nodules at baseline or at follow-up screening.[5–9,12,13] There are only limited data concerning the relationship of the number of nodules detected in a participant (or nodule count) and lung cancer probability. For nodules detected at baseline screening, a recent analysis of the largest European lung cancer screening trial indicated that the baseline nodule count alone does not predict lung cancer.[15] On nodule level, one large study indicated a negative association between the nodule count and a baseline nodule's lung cancer probability when assessed together with other known risk-factors, also reflecting the low incidence of double malignancies.[12]

During a lung cancer screening program, annually in 3-13% of participants new nodules are detected that were not present at baseline screening.[5,16–19] Recently, it was shown that new nodules carry a higher lung cancer probability at smaller size than do baseline nodules.[19] However, an array of non-malignant diseases may be associated with the development of new lung nodules and some participants may tend to develop multiple benign lung nodules of varying size.[9,20] The appropriate risk-stratification of new nodules is important to a lung cancer screening program, as they account for a significant proportion of lung cancers found after the baseline round.[19,21,22] Till recently most research focused on nodules detected at baseline

screening and there is only limited evidence on the management of new nodules.[1,11,19] In a current European position statement on lung cancer screening, it was stressed that the management of new nodules should be different from baseline nodules since they have a higher pretest probability which was also adopted in the British Thoracic Society Guidelines for the Investigation and Management of Pulmonary Nodules.[22] At present, there is no evidence regarding an association of the new nodule count after baseline lung cancer screening and the development of new nodule lung cancer. Aim of this study was to assess the relationship of a participant's number of new nodules and the new nodule lung cancer probability, using data from the largest European randomized controlled lung cancer screening trial.

Material and methods

Study Population

The Dutch-Belgian Randomized Lung Cancer Screening (acronym NELSON, trial registration number: ISRCTN63545820) trial's study design and recruitment process have been published previously.[7,23,24] Briefly, (ex-) smokers aged 50-75, who had smoked at least 15 cigarettes daily for 25 years or 10 cigarettes daily for 30 years and were still smoking or stopped smoking less than 10 years ago were eligible. The Ethics committees of all participating centers approved the NELSON trial. All participants provided their written informed consent. Between April 2004 and December 2006, 7,557 participants underwent baseline screening. The subsequent incidence screening rounds took place 1 year, 3 years, and 5.5 years after baseline screening. The current study included participants in whom the NELSON radiologists registered a new noncalcified nodule during the three incidence screening rounds.

CT Scanning Protocol and image reading

Low-dose CT scans were performed at one of four screening sites using 16-MDCT scanners or 64-MDCT scanners (Sensation-16, Siemens Medical Solutions, Forchheim, Germany; or Mx8000 IDT or Brilliance 16P, Philips Medical Systems, Best, Netherlands). Depending on the participant's body weight (<50kg, 50-80kg, or >80kg), low-dose settings (80-90kVp, 120kVp, and 140kVp) were adapted to match a dose index volume of 0.8mGy, 1.6mGy, or 3.2mGy respectively. Datasets were derived from images of the thorax with 1.0mm slice width and a 0.7mm reconstruction interval.

The data acquisition and imagining protocols were standard across screening sites [7,23]. CT-image analysis occurred on digital workstations (Leonardo, Siemens Medical Solutions) which enabled semiautomated volume analysis using software (LungCare, version Somaris/5 VA70C-W, Siemens Medical Solutions). Image reading was performed by two independent radiologists in the first two rounds and by one radiologist in the third and fourth round, after it was demonstrated that reading consensus provides no benefit with the use of semiautomated software.[25] In case of high suspicion of malignancy (eg, enlarged mediastinal lymph nodes) or benignity (eg, benign calcification patterns), radiologist could overrule protocol-based screening results (as done for 195 [6%] of 3,318 participants at the baseline screening round) and adjust the nodule volume in case of inappropriate segmentation.[26] Detected nodules were matched to previous scans by the software's algorithm and matching was visually confirmed by the radiologist. Data generated during CT evaluation were immediately uploaded to the NELSON management system. This study included data and measurements as uploaded to the NELSON management system and no new or repeat measurements were performed. Nodules were considered new if labeled as new and not present on previous scans by the NELSON radiologists.

Nodule Management Protocol

The detailed NELSON nodule management protocol was published previously.[23] At first detection, new nodules were classified into four categories according to their size and characteristics (NODCAT I-IV). Calcified nodules and nodules with other benign characteristics were considered benign (NODCAT I). New solid nodules measuring 15-50mm^3 and new subsolid nodules with diameter 4-8mm (NODCAT II, follow-up LDCT within one year) as well as new solid nodules 50-500mm^3 and new subsolid nodules ≥8 mm (NODCAT III, follow up LDCT within six-eight weeks) were considered indeterminate, requiring nodule growth assessment. New solid nodules ≥500mm^3 (NODCAT IV, immediate referral to pulmonologist) were considered positive.

Outcomes

A nodule was classified as lung cancer when it was diagnosed as lung cancer during diagnostic workup according to national and international guidelines including histologic examination.[23] Nodules were classified as benign when either: (a) the nodule was benign at histologic examination; (b) extensive workup by a pulmonologist,

including contrast material–enhanced CT, PET, and bronchial washing, had a negative finding; (c) the nodule was ruled negative during the participant's last follow-up in the NELSON trial. As far as accessible in this ongoing trial, data was linked with the Dutch and Belgian national cancer registries and medical files reviewed concerning the occurrence of post-screening lung cancer (completed for the second and third incidence screening round) .[21,23,27]

Nodule counts

For this study two nodule counts were calculated for each participant. First, the number of new noncalcified nodules detected simultaneously at a participant's first new nodule detection after baseline and second, the number of noncalcified nodules detected at baseline screening. The new nodule count may reflect the presence of non-malignant disease. The baseline nodule count might also reflect a participant's tendency to develop nodules.

Statistical Analysis

Normality of continuous variables was evaluated through the Kolmogorov–Smirnov test and visual assessment. All included continuous variables were non-normally distributed and are presented as median and interquartile range (IQR). Categorical variables are shown as frequencies and respective percentages. The Agresti-Coull method was used to calculate 95% confidence intervals (95%CI) of proportions. The correlation of the participant's new nodule count and the participant's age at baseline, the smoking pack-years at baseline, the volume of the largest nodule and the volume of all new nodules was assessed using Spearman's rank correlation. Categorical variables stratified by the new nodule count (0, 1, 2, 3, 4, ≥5) were assessed using Fisher's exact test or the χ^2 test as appropriate. The Mann–Whitney U test was used for comparison of nodule volume between two groups. The discriminative performance of the nodule count with new nodule lung cancer as outcome was evaluated through construction of the area under the receiver-operating-characteristic curve (AUC). To evaluate new nodule count as predictor for new nodule lung cancer together with largest new nodule size (i.e. one case per participant), multivariable logistic regression analysis was performed including new nodule count and size (highest new nodule NODCAT classification and largest new solid nodule volume respectively). In participants where the largest new nodule could not be established based on the exact

volume measurement (1% [10/705]), the nodule with the highest NODCAT classification was considered largest. The model calibration was assessed by a Hosmer-Lemeshow goodness-of-fit test and through comparison of observed and predicted probabilities. Statistical analyses were performed with SPSS version 24.0 (IBM, Armonk, NY, USA), Medcalc version 17.1 (Medcalc Software, Mariakerke, Belgium), and Microsoft Excel (Microsoft Corporation, Redmond, WA, USA).

Results

In total, 705 participants with 964 new nodules were included (Figure 1). Participant characteristics are presented in Table 1. Median participant age at baseline was 59 years (IQR 55-63 years) and 79% (558/705) of participants were male. Subsolid new nodules were detected in 6% (49/705) of participants and 5% (3/65) of the new nodule lung cancers were found in subsolid lesions. In 48% (336/705) of participants no nodule had been found previously during baseline screening and in 22% (154/705) of participants >1 new nodule was detected (range 1-12 new nodules). Eventually, 9% (65/705) of the participants were diagnosed with lung cancer in one of the detected new nodules. In all participants with new nodule lung cancer, the largest (14% [9/65]) or only (86% [56/65]) new nodule was diagnosed as lung cancer.

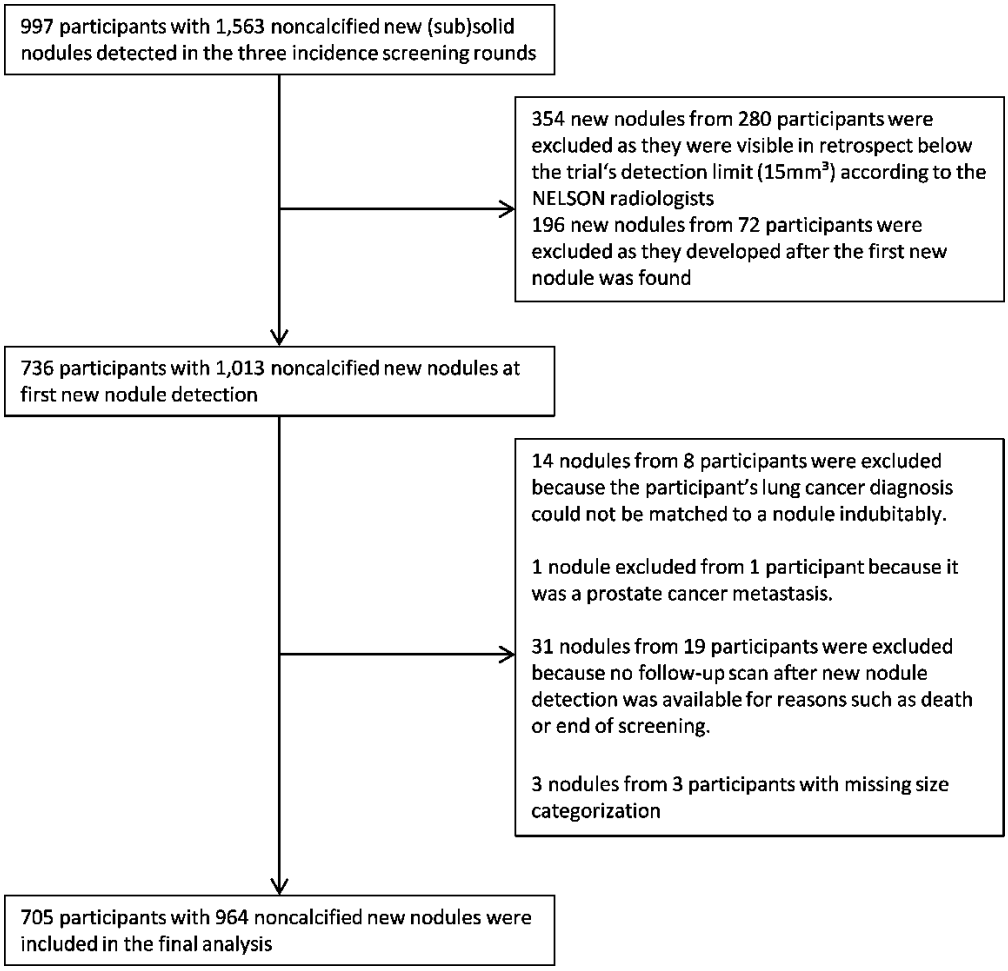

Figure 1: Flowchart of participants and new nodules included in the analysis

	All participants	Number of new nodules detected simultaneously in a participant					
		1	2	3	4	≥5	P-Value
	705 (100%)	551 (78%)	99 (14%)	31 (4%)	13 (2%)	11 (2%)	
Male sex (%)	558/705 (79)	442/551 (80)	72/99 (73)	23/31 (74)	12/13 (92)	9/11 (82)	0.334
Age at baseline							
Median	59	59	59	58	62	61	0.794
IQR	55-63	55-63	55-62	54-65	57-66	57-72	
Pack-years at baseline							
Median	39	39	39	44	49	34	0.455
IQR	30-53	30-53	30-49	38-56	27-58	31-38	
New subsolid nodule (%)	49/705 (6)	35/551 (6)	8/99 (8)	2/31 (6)	1/13 (8)	3/11 (27)	0.131

Table 1: Participant characteristics stratified by number of new nodules detected
Abbreviations: IQR - Interquartile range.

On participant level, receiver operating curve analysis demonstrated no significant predictive ability of the new nodule count for lung cancer (AUC 0.55, 95%CI 0.48-0.62). A participant's overall new nodule lung cancer probability did not significantly differ between participants with 1 new nodule (10% [56/551], 95%CI 8-13%) or >1 new nodule (6% [9/154], 95%CI 3-11%, P=0.116). Participants with multiple new nodules that clustered in one lung lobe had a lower but not statistically different lung cancer frequency when compared to participants with multiple new nodules but no clustering (2% [1/44] vs. 7% [8/110), P=0.232). On nodule level, a lower number of simultaneously detected new nodules showed a moderate predictive ability for lung cancer (AUC 0.67, 95%CI 0.61-0.72) with no double cancers being detected. The participant's nodule count at baseline screening demonstrated no significant discriminative performance for new nodule lung cancer, neither participant level (AUC 0.52, 95%CI 0.45-0.59) nor nodule level (AUC 0.53, 95%CI 0.46-0.60).

The nodule size and lung cancer probability stratified by the participant's number of new nodules are shown in Table 2. While the median volume of the participant's largest nodule increased significantly with more new nodules detected (P<0.001, Spearman's rho 0.177), the lung cancer probability remained equivalent (P=0.63). The lung cancer probability of participants in whom the only detected new nodule was NODCAT III or IV was significantly higher compared to participants with NODCAT III or IV nodules but >1 new nodule detected (15% [50/333], 95%CI 12-19% vs. 8% [9/119], 95%CI 4-14%, P=0.04). When adjusted for the size of the largest new (solid) nodule (Table 3), the new nodule count was a significant predictor, having a negative association with new nodule lung cancer.

		Number of new nodules detected simultaneously in a participant					
	All participants	**1**	**2**	**3**	**4**	**≥5**	**P-Value**
Size classification of largest new nodule[a]							0.002
NODCAT II	253/705 (36)	218/551 (40)	26/99 (26)	7/31 (23)	2/13 (15)	0	
NODCAT III	327/705 (46)	238/551 (43)	57/99 (58)	18/31 (58)	8/13 (62)	6/11 (55)	
NODCAT IV	125/705 (18)	95/551 (17)	16/99 (16)	6/31 (19)	3/13 (23)	5/11 (45)	
Median volume in mm^3							
All new nodules (IQR)	66 (32-188)	68 (33-204)	70 (32-166)	60 (28-206)	50 (27-129)	82 (35-298)	0.352
Largest new nodule (IQR)	84 (37-251)	68 (33-204)	125 (48-257)	165 (61-410)	124 (50-223)	380 (117-1021)	<0.001[b]
Lung cancer							
n/N (%)	65/705 (9)	56/551 (10)	7/99 (7)	1/31 (3)	1/13 (8)	0/11 (0)	0.63
95% CI	7-12	8-13	3-14	0-18	0-35	0-30	

Table 2: Nodule size and new nodule lung cancer probability stratified by number of new nodules detected

Abbreviations: CI - Confidence interval, IQR - Interquartile range.

[a] NODCAT II, Solid nodules measuring 15-50mm^3 and subsolid nodules with diameter 4-8mm; NODCAT III, solid nodules 50-500mm^3 and subsolid nodules ≥8 mm; NODCAT IV, solid nodules ≥500mm^3

[b] Spearman's rho 0.177

Participants with a new (sub)solid nodule				
	Univariate analysis		**Multivariate analysis**	
	Odds ratio (95% CI)	**P-value**	**Odds ratio (95% CI)**	**P-value**
Number of new nodules	**0.67 (0.42-1.07)**	**0.093**	**0.59 (0.37-0.95)**	**0.030**
Size classification of largest new nodule				
NODCAT II			Reference	
NODCAT III			3.9 (1.58-9.65)	0.003
NODCAT IV			16.5 (6.67-40.93)	<0.001
Participant with a new solid nodule				
	Univariate analysis		**Multivariate analysis**	
	Odds ratio (95% CI)	**P-value**	**Odds ratio (95% CI)**	**P-value**
Number of new nodules	0.60 (0.34-1.04)	0.07	0.37 (0.17-0.77)	0.008
Size of largest new solid nodule				
Ln-Volume			2.31 (1.86-2.91)	<0.001

Table 3: Number of new nodules in the prediction of new nodule lung cancer
Abbreviations: CI - Confidence interval.
[a] NODCAT II, Solid nodules measuring 15-50mm^3 and subsolid nodules with diameter 4-8mm; NODCAT III, solid nodules 50-500mm^3 and subsolid nodules ≥8 mm; NODCAT IV, solid nodules ≥500mm^3

Discussion

This analysis focused on participants with new nodules detected during the three incidence rounds of the NELSON trial. We assessed the relationship between the number of new nodules detected in a participant and the probability of developing lung cancer in a new nodule.

There are five major findings. First, in 22% (154/705) of participants more than one new nodule was detected at initial new nodule detection. Second, the lung cancer probability, did not differ significantly between participants with one and more than one new nodule. Third, an increased number of new nodules was correlated with a greater largest new nodule size. Fourth, the new nodule count had a significant negative association with new nodule lung cancer when assessed together with nodule size. Fifth, the participant's overall nodule count at baseline screening was not significantly associated with new nodule lung cancer.

To our knowledge, this is the first study providing evidence concerning a possible impact of a participant's nodule count and the lung cancer probability in new solid nodules. Lung cancer screening participants only have one baseline screen, but potentially many incidence screenings and with increasing duration, a program's success depends on the management of new nodules. Contrary to baseline nodules, which may have been present for years, new nodules develop in a known timeframe

and comprise a group of comparably young nodules.[19] A study focusing on the development of a lung cancer risk model for baseline nodules reported a reduced lung cancer probability with an increasing number of baseline nodules.[12] The findings of this study show similar results for new nodules on nodule level. Nevertheless, on participant level the new nodule count alone showed limited discriminative performance for new nodule lung cancer (AUC 0.55, 95%CI 0.48-0.62). This is comparable to a recent analysis of the NELSON baseline round, where baseline lung cancer probability did not differ significantly per baseline nodule count.[15] However, the here presented findings indicate that in combination with new nodule size the new nodule count has a significant negative association with new nodule lung cancer. This may be explained through the observation that an increased new nodule count is associated with a greater size of the largest nodule found in a participant, while the lung cancer probability remains at least equivalent.

At initial nodule detection and before growth assessment is feasible, nodule size is the most important predictor for lung cancer in both baseline and new nodules and is used for risk-stratification in present guidelines.[10,11,19,22] Currently, the management of detected nodules in lung cancer screening and clinical practice, focusses on the most suspicious or typically largest nodule detected.[10,11,19,22] This reflects a participant-based approach with a theoretical lung cancer probability of smaller nodules not taken into account. The findings of this study show that factoring in the new nodule count could adapt a participant's lung cancer risk stratification in a multivariate approach that includes the largest nodule size. However, additional data is needed to confirm these findings and assess new nodule count together with other risk factors.

This study has limitations. The NELSON trial's detection limit was 15mm^3 and smaller new nodules could not be considered in this analysis. However, newly detected nodules above 15mm^3 and visible below the studies detection limit on a previous scan were excluded. Further, the expertise of radiologist was shown to decrease false-positive screening results.[26] Radiologists potentially increased their expertise in distinguishing scars or infections from suspicious lesions during the trial and could have refrained from classifying them as suspicious nodules to avoid false-positive results. We cannot exclude the possibility that the actual number of new nodules is slightly higher than reported in the NELSON management system. Within the

NELSON management protocol, larger nodules potentially received an additional follow-up LDCT or were referred for further diagnostic work-up. To minimize bias through the protocol, this analysis incorporated all follow-up data of a nodule within the NELSON trial including cancer diagnosis in later rounds and information from the national cancer registries concerning post-screening lung cancer.

Conclusion

In around one-fifth of participants with new nodules in incidence lung cancer screening rounds, more than one new nodule is present. A participant's number of new nodules alone only provides limited discriminatory information for new nodule lung cancer probability. However, with an increasing number of new nodules, the largest new nodule tends to be bigger, while the participant's overall new nodule lung cancer probability remains equivalent. Therefore, relating the largest new nodule size with the number of new nodules found could adjust a participant's lung cancer risk based on the largest nodule size only.

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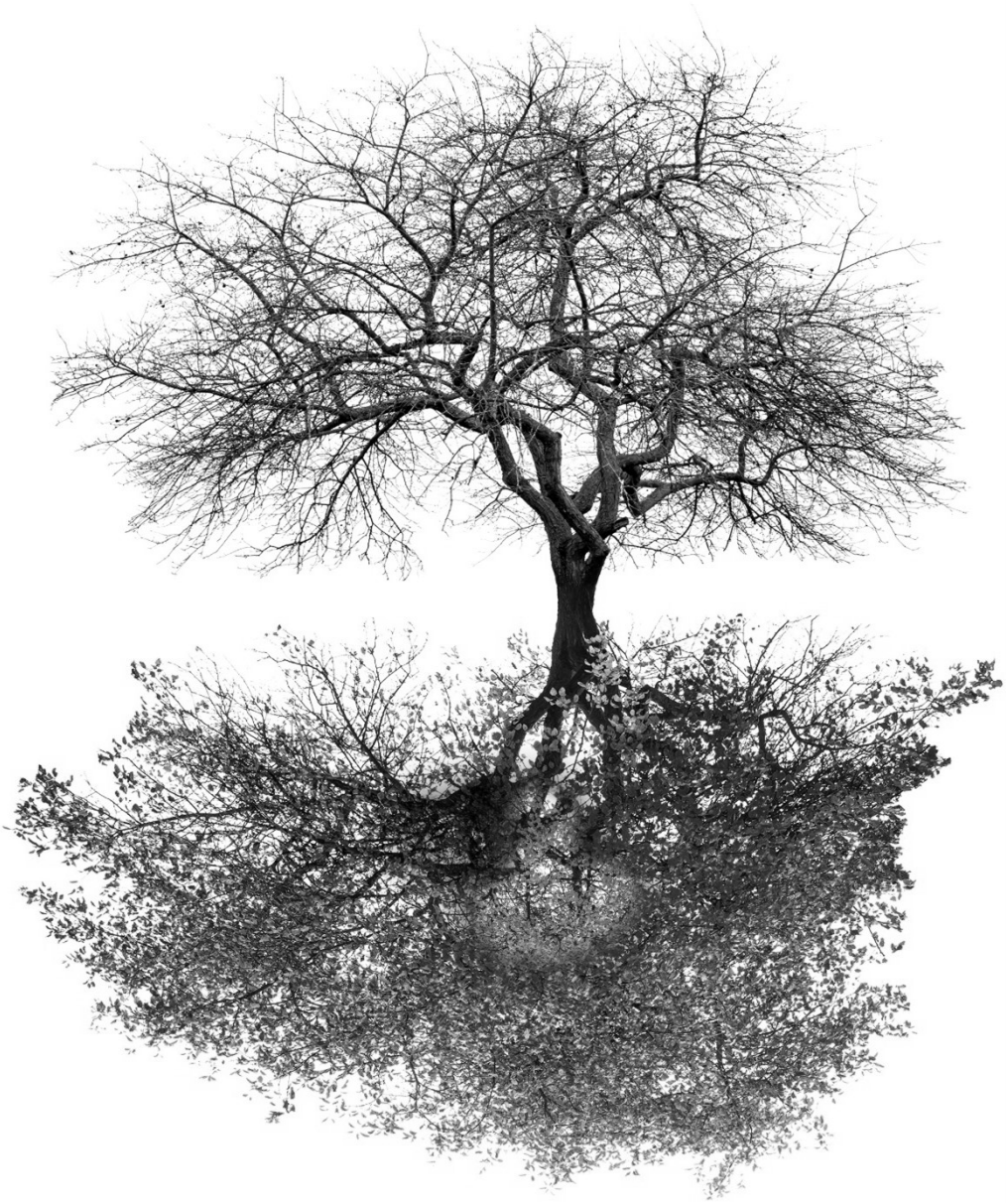
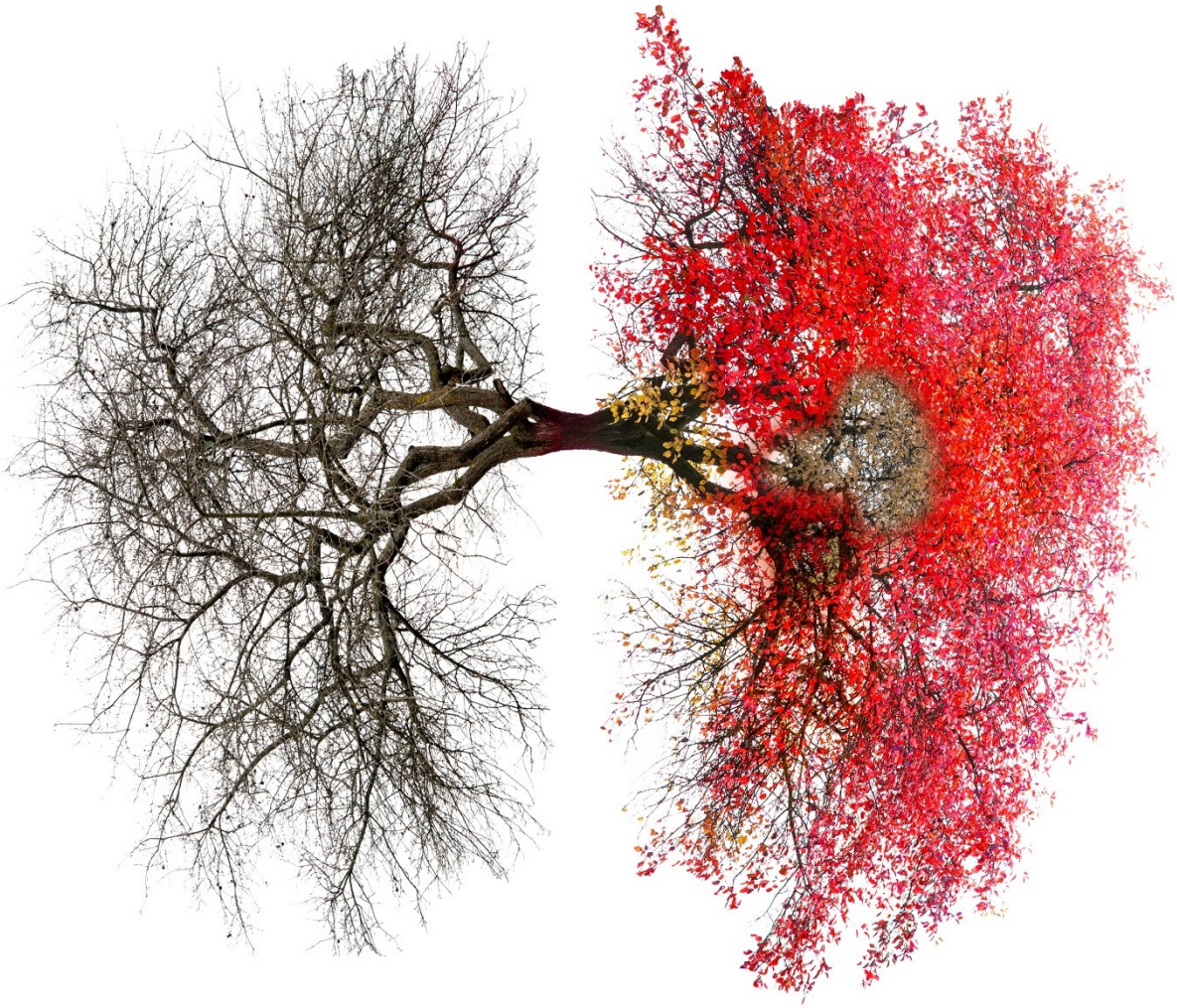


Part IV
General Discussion and Summary



Chapter 10

General discussion and conclusion

The general discussion evaluates and summarizes the main findings of this thesis and presents a list of conclusions with general recommendations for new nodule risk-stratification. Finally, the impact of the thesis until now is briefly reviewed and future perspectives presented.

Lung cancer screening by LDCT is recommended in the United States and experts have recommended to prepare for the potential commencement in Europe.[1] Furthermore, with increasing availability of high-end medical care, incidentally found pulmonary lung nodules are increasingly common in clinical practice.[2] Lung cancer screening with LDCT consists of one baseline screening round and multiple incidence screening rounds.[3,4] Furthermore, participants with suspicious nodules might receive additional follow-up within one round.[5,6] Current nodule risk-stratification protocols are mainly based on nodule size at first detection and nodule growth in subsequent screening rounds.[1,7–10] Appropriate risk-stratification and thus the accurate identification of high-risk participants that require immediate referral for diagnostic work-up as well as the identification of low-risk participants is key to any screening program. Underestimating the risk may cause delayed lung cancer diagnosis, thereby effectively increasing the mortality of participants.[2,11,12] Conversely, a risk overestimation may cause unnecessary and potentially harmful procedures.[13–15]

Nodules detected at baseline potentially have been present for years, whereas nodules newly developed after baseline are possibly fast-growing. Although this is a very intuitive concept, prior to this thesis, there was only very limited evidence concerning the risk-stratification of new nodules detected after baseline.[9,16,17] New nodule management was mostly based on expert-opinion or data derived from baseline nodules.[6–9,16] Recognizing this, this thesis investigated the appropriate risk-stratification of new nodules based on data of the incidence screening rounds of the largest European randomized-controlled lung cancer screening trial. The results of this thesis might apply to both, participants in lung cancer screening programs as well as high-risk patients with incidentally detected nodules and comparable risk-factor epidemiology.

Occurrence of New Nodules in Lung Cancer Screening

Considering the results of this thesis and other lung cancer screening trials, it appears that new nodules are regular findings in low-dose CT lung cancer screening. In annual screening, 5% of the NELSON participants developed a new non-calcified solid nodule, while 11% of the NELSON participants developed a new non-calcified solid nodule within the first two incidence screening rounds (3 years after baseline).[17] The annual new solid nodule occurrence was similar to numbers from the ELCAP and IELCAP studies (3% and 5% respectively) as well as the PLuSS trial (7%).[18–20] However, the location and screening population compositing can impact the occurrence of new nodules significantly. Exemplifying this, the Mayo trial, being conducted in an area with a high prevalence of histoplasmosis, reported a high annual occurrence of new nodules in >10% of participants annually.[21,22] In response to the NELSON trial's results, an analysis of the NLST reported an annual incidence of new nodules in around 3% of participants (note: only nodules ≥4mm were registered as compared to 15 mm³ [around 3mm] in the NELSON trial).[23] Nevertheless, these numbers are limited in their direct comparability, as new nodules were defined differently within trials and rates have not been reported explicitly.[16,24] However, new nodules are consistently found in lung cancer screening trials. Importantly, the frequency of new nodule detection is not directly linear with screening interval length. In the NELSON trial, 5% of participants presented with new solid nodules in the second screening round (1 year after baseline) but only 7% of participants had new solid nodules in the third screening round (3 years after baseline).[17] This will be further explored in a subsequent section of this discussion.

Compared to new solid nodules, non-solid new nodules are less common. New subsolid nodules were found in <1% of participants with at least one screening after baseline.[25] This is comparable to findings of the I-ELCAP trial, where <1% of participants presented with new part-solid or new non-solid nodules respectively.[26,27]

Thus, new lung nodules should be expected in any lung cancer screening program. This particularly underscores the need to register every observable nodule in a participant and not only the most prominent. The meticulous identification of new nodules is key for any risk-stratification strategy to be implemented.

Lung Cancer Probability of New Nodules in Lung Cancer Screening

As shown in this thesis, new solid nodules have already at smaller size a higher lung cancer frequency as compared to nodules present at baseline, but LDCT lung cancer screening enables the detection of new nodule lung cancer at an early stage. Conversely, new subsolid nodules have a lung cancer frequency and course comparable to subsolid baseline nodules.

In this thesis it was found that 6% of participants with a new non-calcified solid nodule developed lung cancer in such a nodule, with 4% of the new solid nodules proving to be lung cancer.[17] In a previous analysis of the NELSON trial, 1% of participants were detected with lung cancer during the baseline screening round,[5] and for the first three rounds it was reported that approximately 3% of participants were detected with lung cancer (including new nodule cancer).[28] The ELCAP trial reported that 10% of participants with new non-calcified pulmonary incident nodules on LDCT had lung cancer in a new nodule, and the IELCAP reported this was the case for 5% of its participants.[18–20] In response to the NELSON trial's analysis, data of the NLST confirmed the results, with 6% of the new solid nodules being lung cancer as compared to only 3% of the baseline solid nodules.[23,29] Of the detected new solid lung cancers in the NELSON trial, 38% were adenocarcinomas, 22% were squamous-cell carcinoma, and 10% were small-cell lung cancer.[17] To our knowledge, until its publication, the NELSON trial was the first to provide specific data concerning new solid nodule lung cancer stage and histology.[17,24] The NLST trial reported that 27% of new solid nodule lung cancer were adenocarcinoma and 16% were small-cell lung cancer.[23] In the NELSON trial, it was found that 68% of the new solid nodule lung cancers were detected at stage I which was comparable to baseline screening (64%).[17] The IELCAP trial reported that 86% of lung cancers in patients with a new non-calcified pulmonary incident nodule was detected at stage I, whereas the NLST trial found 60% of new solid nodule lung cancer at stage I.[19,23] Thus, LDCT lung cancer screening enables the early detection of new nodule lung cancer.

Here it was found that 6% of participants with a new subsolid nodule had a lung cancer diagnosed in such a nodule, with 5% of the new subsolid nodules being lung cancer.[25] Until now the I-ELCAP is the only other trial that reported new subsolid nodule lung cancer frequencies.[30,31] Overall, 4% of the new subsolid nodules detected in the I-ELCAP trial were lung cancer.[26,27] All new subsolid nodule lung cancers detected in

the NELSON trial were stage I or adenocarcinoma in situ.[25] This is comparable to results of the I-ELCAP trial where all new subsolid lung cancer cases were stage I.[26,27] Additionally, previous prospective Japanese studies reported that all pathologically confirmed tumors in subsolid nodules were stage I and ≤1% of subsolid nodules were invasive adenocarcinomas.[32,33] Furthermore, an analysis of lung cancer manifesting as nonsolid nodule (baseline and incident clustered together) in the NLST concluded that annual follow-up is appropriate.[34]

The high lung cancer probability of new solid nodules as well as their relatively frequent occurrence in lung cancer screening underlines the need for an appropriate risk-stratification strategy. However, the presented results also demonstrate that LDCT lung cancer screening enables the detection of new nodule lung cancer at an early stage. In the fourth screening round of the NELSON trial, 5.5 years after baseline screening, the majority of lung cancers was found in new nodules.[35] Moreover, around half of lung cancers in the NELSON trial were found in participants with previously negative screening results.[35] This stresses the significance of new nodules detected in lung cancer screening. With ongoing duration, the appropriate management and risk-stratification of new nodules will determine the success of a screening program.

Risk-stratification of New Solid Nodules at Initial Detection

Considering the findings presented in this thesis, new solid nodules have a higher lung cancer probability than baseline nodules at smaller size. Size cutoff values derived from baseline nodules or mixed-nodule groups potentially underestimate the lung cancer risk of new solid nodules. At initial detection, a low-risk cutoff of 30mm^3 and a high-risk cutoff of 200mm^3 can be used to stratify new solid nodules in LDCT lung cancer screening.

There only is little evidence from other lung cancer screening trials concerning the stratification of new solid nodules. As presented in this thesis, new nodule size at initial detection provided moderate to high discriminative ability for lung cancer.[17] Comparing the second screening round (1 year screening interval) and the third screening round (2 year screening interval), the discriminative ability increased with a longer screening interval.[17] This suggests that new nodules need time to grow in order to be evaluated based on size only, making growth speed measures such as the volume doubling time crucial for follow-up assessment. Nodule volume provided superior discriminative

ability when compared to the computer simulated mean nodule diameter. Moreover, as manual diameter measurements are even less precise and reproducible,[36,37] they might have performed even worse.

The new solid nodule lung cancer probability is high at a small size, especially in comparison with nodules detected at baseline.[17] Prior to the presented studies, data of the NELSON trial suggested that baseline nodules smaller than 100mm³ had a lung cancer probability of about 0.6%, were not predictive of lung cancer, and did not necessitate additional follow-up scans.[28,38,39] However, this criterion does not apply in the case of new solid nodules. As shown in this thesis, 3% of participants whose largest new solid nodule was smaller than 100mm³ were eventually diagnosed with lung cancer, with 2% of new solid nodules smaller than 100mm³ found to be lung cancer.[17] These findings were later confirmed by an analysis of the NLST which, at smaller size, reported a significantly higher lung cancer risk in new solid nodules as compared to baseline nodules.[23] The optimized volume cutoffs for new solid nodules were <27mm^3 (<1% lung cancer probability, low risk), 27-206mm^3 (3% lung cancer probability, intermediate risk), and ≥206mm^3 (17% lung cancer probability, high risk), providing 95% sensitivity.[17] It has been proposed by a European expert group to adapt these cutoffs for clinical implementation to 30mm^3 and 200mm^3 respectively.[1] The optimized computer simulated mean diameter cutoffs were <3.7mm (<1% lung cancer probability, low risk), 3.7-8.2mm (3% lung cancer probability, intermediate risk), and ≥8.2mm (14% lung cancer probability, high risk), providing 95% sensitivity.[17] These probabilities are in concordance with lung cancer probabilities for the respective American College of Radiologists Lung-RADS categories.[8] However, these diameters represent simulated diameter measurements of new nodules, extrapolated from computer-generated volume measurements based on three-dimensional voxel analysis,[1,40] with manual diameter measurements being less precise or reproducible.[36]

The results of the NELSON trial were subsequently confirmed by data of the NLST.[23] It was found that especially at very small size, the lung cancer risk between new solid nodules and baseline nodules differed markedly: 4-6mm mean diameter (2.3% vs. 0.4%, 6 times higher) and 6-8mm mean diameter (5.4% vs. 1.3%, 4 times higher).[23] Even more remarkably, while the NLST did not include nodules with a longest diameter <4mm (around 34mm^3) and therefore cannot represent these nodules accurately, the researchers reported a significantly higher lung cancer risk in nodules with a mean diameter <4mm (1.1% vs. 0.1%).[23] In light of these results, the currently advocated,

new solid nodule size diameter cutoff in LungRADs of 4mm,[8] should be reviewed to assess whether it appropriately represents the actual lung cancer risk of new solid nodules.

In the NELSON trial, around 60% of new solid nodules detected were smaller than 50mm^3 (roughly 4.5mm).[17,24] The ELCAP and Mayo trial reported similar numbers between 40-55% for new nodules smaller than 5mm and 4mm respectively.[18,21] At these tiny nodule sizes, growth detection based on two-dimensional diameter evaluation is unreliable,[31] favoring volumetry. It was found that already for intermediate sized nodules (50-500mm^3, roughly 4.5-10mm), intra-nodular diameter variation, varied by 2.8mm which is above the 1.5mm cutoff for nodule growth currently employed in the United States.[41] Furthermore, even a computer simulated mean diameter provided inferior performance for new nodule risk-stratification when compared to semi-automated volume measurement.[17]

This thesis introduced the concept of a predicted maximum volume doubling time (VDT_{max}) or slowest possible volume doubling time for a new solid nodule at initial detection.[17] It enables a growth speed estimation at initial new nodule detection by accounting for the known time interval in which the new nodule must have developed. It does not represent the actual volume doubling time for which two exact volume measurements at two distinct time points are necessary. In other words, the VDT_{max} corrects the size of a new nodule at initial detection for the time the nodule had to grow. While this might be of limited use in the screening setting, where time intervals are generally predefined, it could be of clinical utility when assessing incidentally detected nodules in patients that have a prior CT scan available in clinical practice. In the presented setting, the estimated VDT_{max} was significantly faster in new nodule lung cancers than in benign new solid nodules and the median VDT_{max} of adenocarcinomas and squamous-cell carcinomas was similar to the previously reported true VDT of fast-growing baseline cancers in the NELSON trial.[42]

Nevertheless, most new solid nodules are small and will receive additional follow-up to determine the necessity for referral.[8,17,23] Consequently, evaluation of growth-speed could further improve risk-stratification of low and intermediate-risk new solid nodules.

Risk-stratification of New Solid Nodules at First Follow-up After Initial Detection

In this thesis, it was found that volume doubling time-based risk-stratification is appropriate for new solid nodules after initial detection. The addition of a volume limit

that confers immediate referral prevents slow growing lung cancers from evading timely referral. Classifying a new solid nodule with either <600days volume doubling time or ≥200mm³ volume positive provides very high sensitivity and specificity for lung cancer with a positive predictive value >25%.

At follow-up after new solid nodule detection, volume provided high and volume doubling time provided very high discrimination for lung cancer.[43] The performance was higher than at initial detection,[17,43] underlining that the discrimination of new nodule lung cancers increases with longer screening time interval. The addition of the previously found high-risk volume cutoff of 200mm^3 further improved discrimination by volume doubling time alone.[43] Of new solid nodules <200mm^3 at initial detection and ≥200mm^3 at first subsequent screening LDCT, 38% were lung cancer and the addition of a volume limit could improve risk stratification also after initial detection.[43] Considering that lung cancer growth was shown to not necessarily be exponential or linear,[44,45] addition of a volume limit compelling referral to a pulmonologist might prevent slow growing lung cancers from evading timely referral.

The optimized volume doubling time cutoff was 590 days and combined with the ≥200mm^3 high-risk cutoff, thereby classifying nodules positive when at least one criterion was fulfilled, provided 100% sensitivity and 84% specificity for discriminating lung cancer.[43] The observed statistically optimal VDT cutoff of ≤590 days is analogous to currently employed cutoffs of ≤600 days, such as in the British Thoracic Society guideline for the investigation and management of pulmonary nodules and the NELSON management protocol,[7,9] and its appropriateness is confirmed for the first time in new solid nodules. However, further research is required to determine whether immediate referral might be appropriate for all low- and intermediate-risk new solid nodules with a VDT ≤600 days (8.3% [1/12] of nodules with VDT 400-600 days and 34% [22/64] of nodules with VDT <400 days).[43]

Importantly, more than half of new nodules resolve until first follow-up after initial detection.[25] In total, 7% of participants with nonresolving low- and intermediate risk new solid nodules (0-3% lung cancer probability based on risk-stratification at initial detection) had lung cancer in such a nodule.[43] We found that with longer screening interval the number of new nodules did not increase proportionally while the percentage of lung cancers further increased.[17] This phenomenon could be explained by the nature of nonresolving new nodules: The longer a screening interval, the higher the proportion of nonresolving new nodules and consequently the higher the

percentage of lung cancers. This is important when assessing new nodules found after different screening interval lengths or during short-term follow-up. A previous study of the NELSON trial examined the disappearance of intraparenchymal solid baseline nodules sized 50-500mm^3 and reported that 90% of the nodules persisted, with 3% of nonresolving nodules being diagnosed as lung cancer eventually.[46] The fact that compared to baseline nodules more new nodules resolve can be explained by the difference of the two nodule groups. Baseline nodules may have been present for years and are therefore more likely to be stable, while new nodules develop within a short, known time-frame and are more likely dynamic. Thus, the mere persistence of a new nodule might be considered as a risk factor for lung cancer.

Number of Nodules and New Nodule Characteristics

Multiple nodules are regularly detected in LDCT lung cancer screening participants. While risk-stratification should be based on the nodule with the greatest risk of malignancy, all nodules need to be assessed carefully to ensure detection of new nodules. Most lung cancers are found in a participant's largest nodule when using volumetry.

Of patients detected with pulmonary nodules, around 50% of participants had more than one nodule at baseline and around 20% had more than one new nodule detected.[47,48] The NLST reported that around 20% of participants had more than one new nodule during two incidence screening rounds.[23] In 97% of patients at baseline and in 100% of patients with new nodules the lung cancer was found in the largest nodule.[47,48] This contrasts with the results by McWilliams et al.,[49] who showed that in one-fifth of the participants, the largest nodule was not the one that turned out to be malignant at baseline or follow-up. This discrepancy might be explained by the use of volumetric measurement in the NELSON study, as compared to manual, two-dimensional diameter measurements in the PanCan study. It has been shown that nodule measurements with volumetric techniques are more accurate as compared to diameter techniques.[36,37,41] Possibly, diameter measurements cannot identify the largest nodule as precise as volumetry. However, while the policy to base screening risk-stratification on the nodule with the highest malignancy risk (often the largest) is confirmed,[1,8] all nodules need to be assessed separately. This ensures the appropriate detection of new nodules which have a higher malignancy risk at smaller size.[17,23] While the new nodule lung cancer probability, did not differ significantly between

participants with one and more than one new nodules, the new nodule count had a significant negative association with new nodule lung cancer when assessed together with nodule size.[48] This may be explained through the observation that an increased new nodule count is associated with a greater size of the largest new nodule found in a participant, without increase in lung cancer probability.

In new solid nodules, nodule characteristics not influenced by nodule growth, such as location in the right upper lung and a central distribution, can potentially improve volume-based risk stratification, but in a three category (low, intermediate and high risk) stratification approach, this is limited. Nodules visible <15mm^3 and at detection >30mm^3 should be considered fast growing and have a high lung cancer risk. To our knowledge there are no comparable studies available for new nodules.
When added to the previously established new solid nodule volume cutoff values (<30mm^3, 30-<200mm^3, ≥200mm^3),[1,17] only growth independent nodule characteristics remained independent predictors for lung cancer.[50] Nodule location in the right upper lung and central distribution provided an incremental value, while nodule shape and margin did not improve lung cancer discrimination.[50] This contrasts findings in baseline nodules, where aside of location, nodule morphology remained significantly associated with lung cancer when corrected for nodule size.[49–52] Importantly, in univariate analysis nodule features traditionally attributed to lung cancer, such as location in the upper lung, central distribution, irregular shape, and a lobulated or spiculated margin, were also associated with lung cancer in new solid nodules.[23,50] This might be explained by the augmented predictive information of nodule size in new solid nodules, which developed in a short and known timeframe, as compared to baseline nodules, that could have been present for years before detection. The volume of a baseline nodule primarily represents its current size, whereas the volume of a new nodule more directly translates to its growth rate. This is supported by the observation that only morphological characteristics forfeit their predictive association through addition of nodule volume, while growth independent features remain significant predictors. Visibility as very small nodule (<15mm$^{3)}$ in retrospect was significantly associated with lung cancer when combined with the volume cutoffs.[45] Nodules visible in retrospect are more likely to be persisting nodules which could explain their higher cancer risk when further growing.[43] Nodules visible in

retrospect <15mm^3 and at detection >30mm^3 have a high cancer risk, even higher than a new nodule not visible at all in retrospect at similar size.[50]

Nevertheless, the identified new solid nodule characteristics did not significantly improve risk stratification by volume when considering a three category (low-, intermediate-, high-risk) stratification approach, such as advocated in current guidelines.[1,8,9,17] However, above risk-thresholds of 2%, growth independent new nodule characteristics can increase the true positive detection rate without affecting the false-positive rate.[50]

Strengths and Limitations of this Thesis

This thesis is based on data from the largest randomized European LDCT lung cancer screening trial, thus mimizing the risk of selection bias. Furthermore, contrary to previous large LDCT lung cancer screening trials, it employed a volume based management approach, thereby registering even very small nodules. Nevertheless, nodules smaller than <15mm^3 were below the trial's detection limit and were not considered when remaining smaller than this margin. While incidentally detected nodules visible in retrospect >15mm^3 were excluded from analysis (missed nodules), nodules visible in retrospect <15mm^3 were included for several reasons. First, due CT resolution limitations, the possiblity of a minuscule nodule being present on a prior screen cannot be excluded for any new nodule. Some nodules might only have become apparent in retrospect since they further grew. Second, prior to this thesis, there was only very limited knowledge on new nodules overall. Omitting a significant proportion of nodules before analysis was not justifiable and would have limited the generalizability of the risk-stratification strategy. Third, sensitivity analyses enabled the confirmation of the obtained findings and risk-stratification approach in the respective new nodule groups. Lastly, these nodules demonstrated potential growth which increased their suspiciousness for lung cancer.

Data used in this thesis based on the NELSON management system as recorded by the NELSON radiologist's during the trial and no additional image reading occured. This approach increased the generalizability of the findings as the actual observations in a screening setting were represented, but a small proportion of misclassified nodules cannot be excluded. Further, the final results of the NELSON trial have not yet been released. While all available follow-up data was used for this study, including the occurrence of post-screening cancers, the lung cancer frequency of new nodules

might be even higher. Screen-detected lung cancers that would have never been clinically detected is a risk of screening and can lead to unnecessary diagnostic work-up procedures and even cancer treatment. To limit this, the risk-stratification strategy developed in this thesis uses risk-categories (low-, intermediate-, and high-risk) as defined in current, well-established lung cancer screening guidelines. Nevertheless, further studies are necessary to determine the degree of overdiagnosis in lung cancer screening.

General Conclusions

I. New nodules are regular findings after baseline lung cancer screening.

II. New solid nodules are more frequent than new subsolid nodules.

III. The number of new nodules detected in participants is not directly proportional to the screening interval length since more than half are resolving nodules.

IV. With increasing screening interval length, the proportion of resolving new nodules decreases and the lung cancer probability increases.

V. New solid nodules have a higher lung cancer probability than baseline nodules, even at a smaller size.

VI. New solid nodules should be followed up more aggressively than baseline nodules by using lower size cutoffs at initial detection.

VII. At follow-up, growth assessment, potentially in combination with a size limit, is appropriate for risk-stratification of new solid nodules.

VIII. Volumetry is preferred over diameter measurement for new nodule risk-stratification.

IX. Risk-stratification of new subsolid nodules can be performed analogous to baseline subsolid nodules.

X. Meticulous lung cancer screening enables detection of new nodule lung cancer at an early stage.

XI. The appropriate risk-stratification of new nodules determines the success of a lung cancer screening in terms of detection of lung cancer at an early stage.

XII. Nodule characteristics do not significantly improve new solid nodule risk stratification by volume when considering a three-category approach.

XIII. Location nodule characteristics, but not morphologic nodule characteristics, can improve lung cancer discrimination in intermediate and high-risk new solid nodules.

XIV. All lung nodules of a participant need to be assessed separately to ensure the detection of new nodules.

XV. Risk-stratification should be based on the nodule with the highest malignancy risk which not necessarily is the largest.

Summarized Recommendations

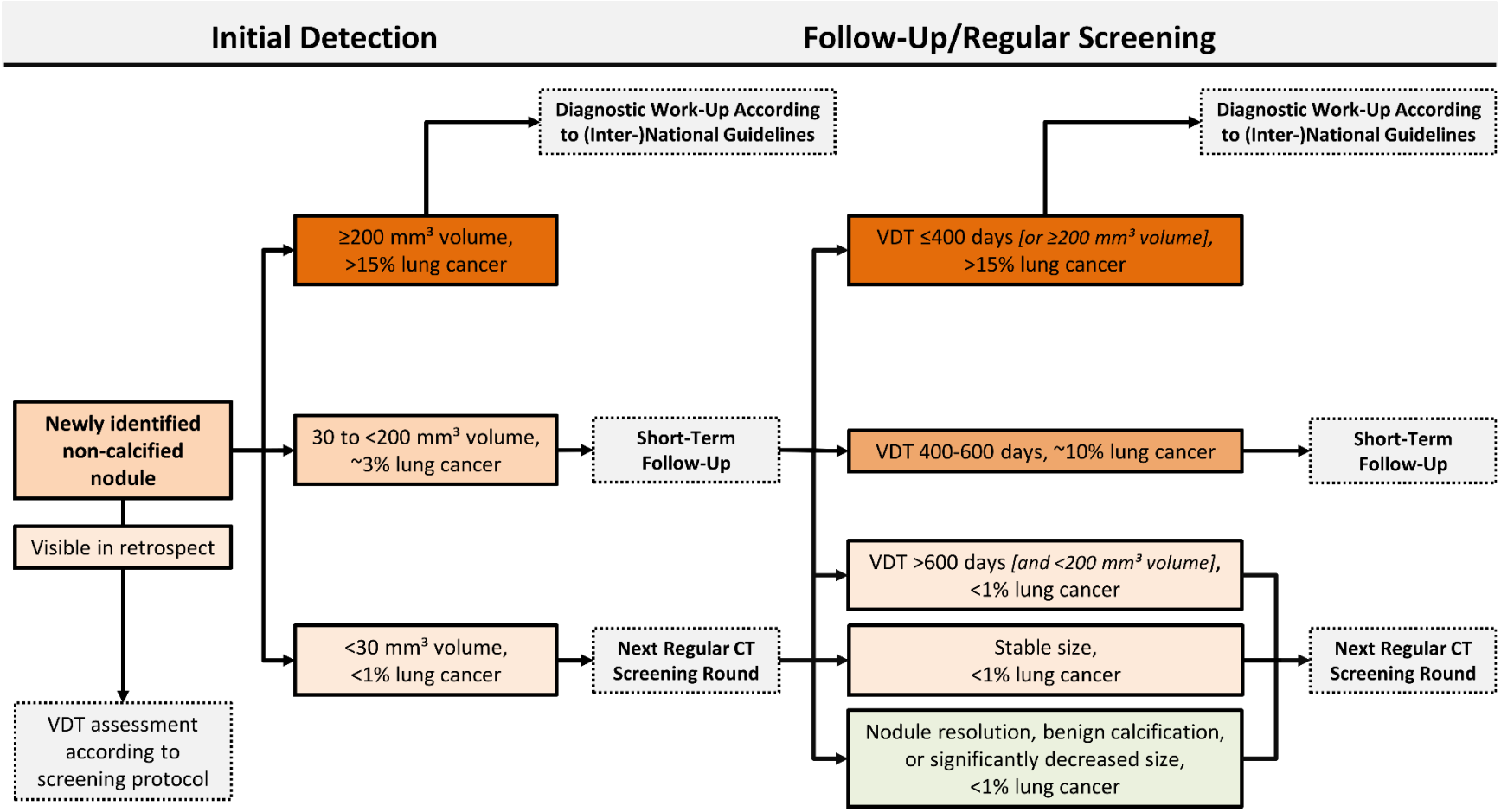


Figure 1: Risk-stratification of new solid nodules detected in low-dose CT lung cancer screening incidence rounds
VDT - Volume doubling time

Generalizability and Clinical Implications

The findings of this thesis are based on data of the randomized NELSON trial conducted in the Netherlands and Belgium which included current or former (quit maximum 10 years ago) smokers (smoked > 15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years) aged 50-75 years, without co-morbidity impeding curative therapy, thereby corresponding to the target population for lung cancer screening.[1] While these data represent the high-risk population of the respective countries and seem well suited to represent similar European populations, any application needs to be carefully evaluated. Differences in epidemiology, inclusion criteria or disease prevalence can affect the optimal risk-stratification strategy. Therefore, some findings, such as size and VDT cutoffs might require re-estimation when the screening population or pretest probability differs substantially. Furthermore, the NELSON trial represents a predominantly Caucasian population. Considering the volume-based management approach, software for semi-automated volume measurements is required. Such packages are provided increasingly with new CT machines, but are not available everywhere. Nevertheless, the general conclusions of this thesis remain unaffected by this. In the clinical practice, the recommendations developed in this thesis could be of use in high-risk patients with similar epidemiology as the population of NELSON trial. Nevertheless, considering the different setting, the final management decision should always reflect clinical expertise. Furthermore, lung cancer screening trials are characterized by pre-defined screening time intervals. In clinical practice, the time period prior to new nodule detection may differ substantially. In these cases, the use of the VDT_{max} could correct for such differences. However, further research is necessary to confirm this with clinical practice data.

Implementation and Future Perspective

In response to the evidence generated in this thesis, the findings were confirmed by data of the largest randomized controlled lung cancer screening worldwide.[23] The conclusions of this thesis and the summarized recommendation were implemented in a European position statement on lung cancer screening and will be implemented in the British Thoracic Society Guidelines for the investigation and management of pulmonary

nodules.[1,53] The summarized recommendation was also included in a Polish consensus statement for the detection of early lung cancer.[54] Furthermore, the new

solid nodule management protocol of the Chinese National Lung Cancer Screening Guideline is partly based on the results of this thesis.[55] The European Society for Medical Oncology clinical practice guidelines for "Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer" argue that findings of this thesis might be of clinical utility in the management of solitary pulmonary nodules detected in clinical practice.[56] Citing results of this thesis as sole reference, the 2018 United States National Comprehensive Cancer Network guidelines on lung cancer screening recommend lower cutoff sizes for new solid nodules.[10]

The final results of the NELSON trial and other European lung cancer screening trials will determine the establishment of lung cancer screening programs in Europe. This thesis makes no assertion concerning the necessity or feasibility of lung cancer screening. However, considering that lung cancer screening is already ongoing in the United States and lung cancer screening studies are being conducted worldwide, future research concerning new nodules is imperative. Next to the conformation and adaptation of the presented findings in other, independent populations, several unanswered questions emerged. First, considering the resolving nature of most new nodules, the impact of the screening interval length on risk-stratification needs to be established. The time until the subsequent screening moment has important implications for the patient but also economic ramifications. Furthermore, findings of this thesis indicate that a too short screening interval potentially impairs lung cancer discrimination based on size. Second, while volumetry was shown to provide significant advantages over manual diameter measurements, the latter remains the most commonly used approach in clinical practice. Therefore, existing diameter-based lung cancer screening trials should further investigate the appropriate diameter risk-stratification of new nodules. Third, as shown in this thesis, new nodule characteristics carry some incremental discriminative information for lung cancer. While their use is limited in the current risk-stratification format, further research is necessary to further evaluate their clinical and screening use. Increasingly, patients in clinical practice have receive multiple CT examinations. The fact whether an incidental nodule is observable in retrospect can be easily obtained in such cases. Fourth, with the rise of advanced modeling techniques and use of artificial intelligence or machine learning, the detection and risk-stratification of (new) nodules could improve considerably. Fifth, the final mortality data of the NELSON trial is not yet available. It will be of great interest

whether there is a mortality difference in participants with baseline lung cancer and new nodule lung cancer.

LDCT lung cancer screening demonstrated that a lung cancer mortality reduction is possible, especially in concert with smoking cessation programs and improved lung cancer treatment modalities. Nevertheless, further research remains the key to explore the full potential of lung cancer screening and optimal new nodule risk-stratification.

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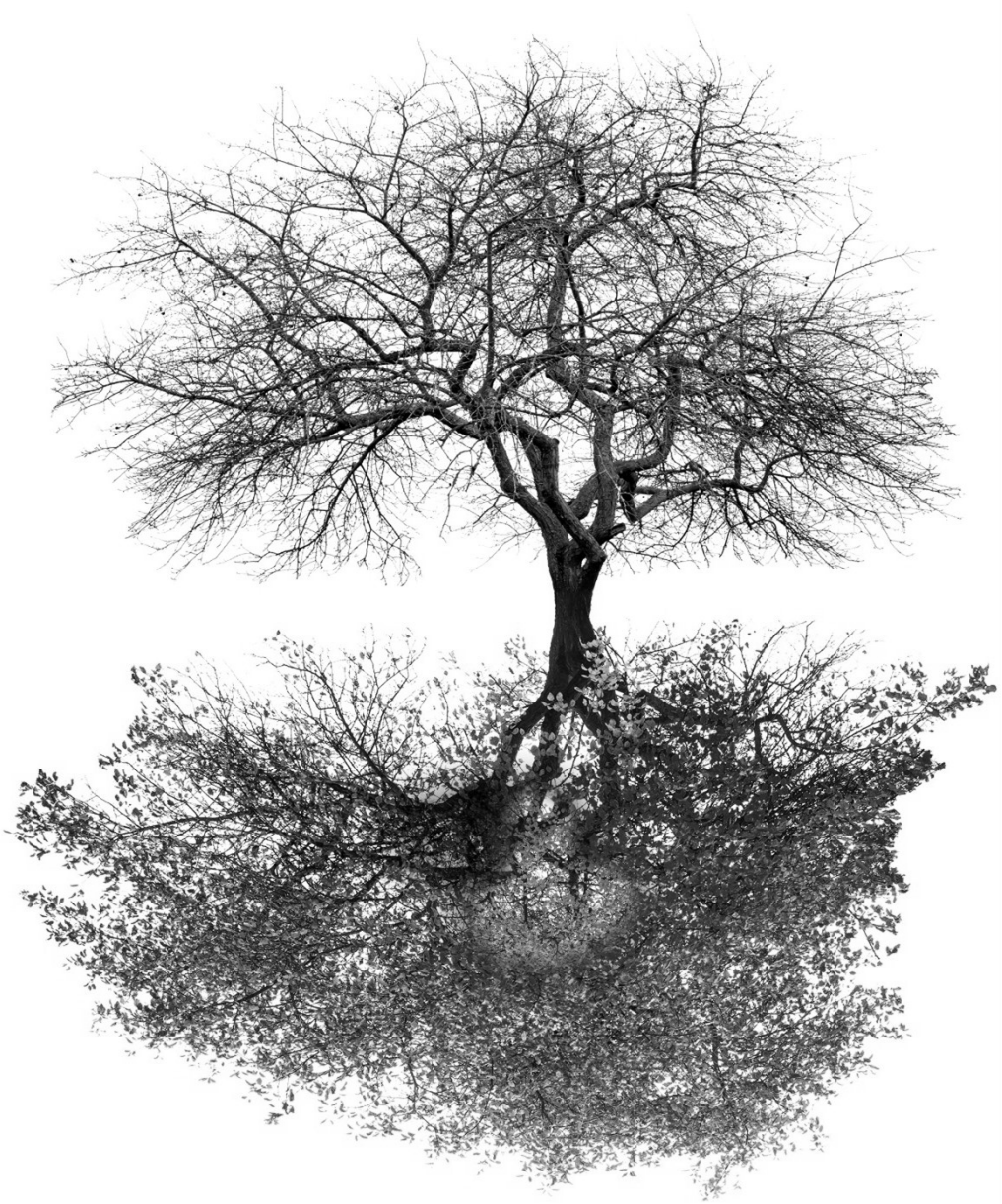


Chapter 11

Summary

New nodules at incidence low-dose CT lung cancer screening

English summary

Part I – Introduction

Lung cancer screening is recommended in the United States and stakeholders are preparing the potential implementation in Europe. Appropriate and accurate risk-stratification is the basis for any successful screening program. It has been recognized that there is limited evidence concerning the risk-stratification of new nodules detected after the baseline screening round of low-dose CT (LDCT) lung cancer screening. The aim of this thesis is to provide evidence for the risk-stratification of new nodules at initial detection and follow-up using data from the largest European randomized controlled lung cancer screening study – the Dutch-Belgian NELSON trial.

In **Chapter 2** and **Chapter 3**, evidence from large lung cancer screening trials is reviewed to create a basis for this thesis. It was found that, while data concerning baseline nodules are consistently reported, definitions of new nodules varied, and new nodule data were often not reported at all. The sparse existing evidence suggests that 3-10% of LDCT lung cancer screening participants develop new nodules annually and that 2-8% of participants develop lung cancer in such a nodule. Compared to baseline nodules which might have been present for years, new nodules develop in a short time interval. This indicates that new nodules might have a higher lung cancer probability than baseline nodules at smaller size.

Part II - Risk-stratification of New Nodules

Chapter 4 assessed the occurrence and lung cancer probability of new solid nodules in the NELSON trial. In annual screening, 5% of the NELSON participants developed a new non-calcified solid nodule, while 11% of the NELSON participants developed a new solid nodule within the first two incidence screening rounds (3 years after baseline). Overall, 6% of participants with a new solid nodule had lung cancer in such a nodule, with 4% of the new nodules being lung cancer. In comparison, in the baseline round of the NELSON trial, 1% of participants were detected with lung cancer and 3% were detected with lung cancer in the first three rounds (including new nodule cancer). The new solid nodule lung cancer probability is high at a small size, especially in comparison with nodules detected at baseline. The optimized volume cutoffs for new solid nodules were <27mm^3 (<1% lung cancer probability, low risk), 27-206mm^3 (3% lung cancer probability, intermediate risk), and ≥206mm^3 (17% lung cancer probability, high risk), providing 95% sensitivity. These cutoffs are smaller than the respective

cutoffs for baseline nodules (<100mm^3, 100-300mm^3, and ≥300mm^3). Summarized, new solid nodules have a higher lung cancer probability than baseline nodules at smaller size and require lower cutoff sizes at initial detection.

Chapter 5 investigated the appropriate risk-stratification strategy of new solid nodules at first screening after initial detection. More than half of new nodules were resolving. Volume provided high and volume doubling time provided very high discrimination for lung cancer. Of new solid nodules <200mm^3 at initial detection and ≥200mm^3 at first subsequent screening, 38% were lung cancer and the addition of a 200mm^3 volume limit improve risk stratification. The optimized volume doubling time cutoff was 590 days and combined with the ≥200mm^3 high-risk cutoff, thereby classifying nodules positive when at least one criterion was fulfilled, 100% sensitivity and 84% specificity for discriminating lung cancer was reached.

In **Chapter 6,** the potential incremental value of nodule characteristics on top of the previously found new solid nodule volume cutoff values (adapted to <30mm^3, 30-<200mm^3, ≥200mm^3) was assessed. Nodule characteristics not influenced by nodule growth, such as location in the right upper lung and a central distribution, could improve volume-based risk stratification and increased the true positive rate without affecting the false-positive rate above risk-thresholds of 2%, but in a three-category stratification approach (low, intermediate and high risk) this was limited.

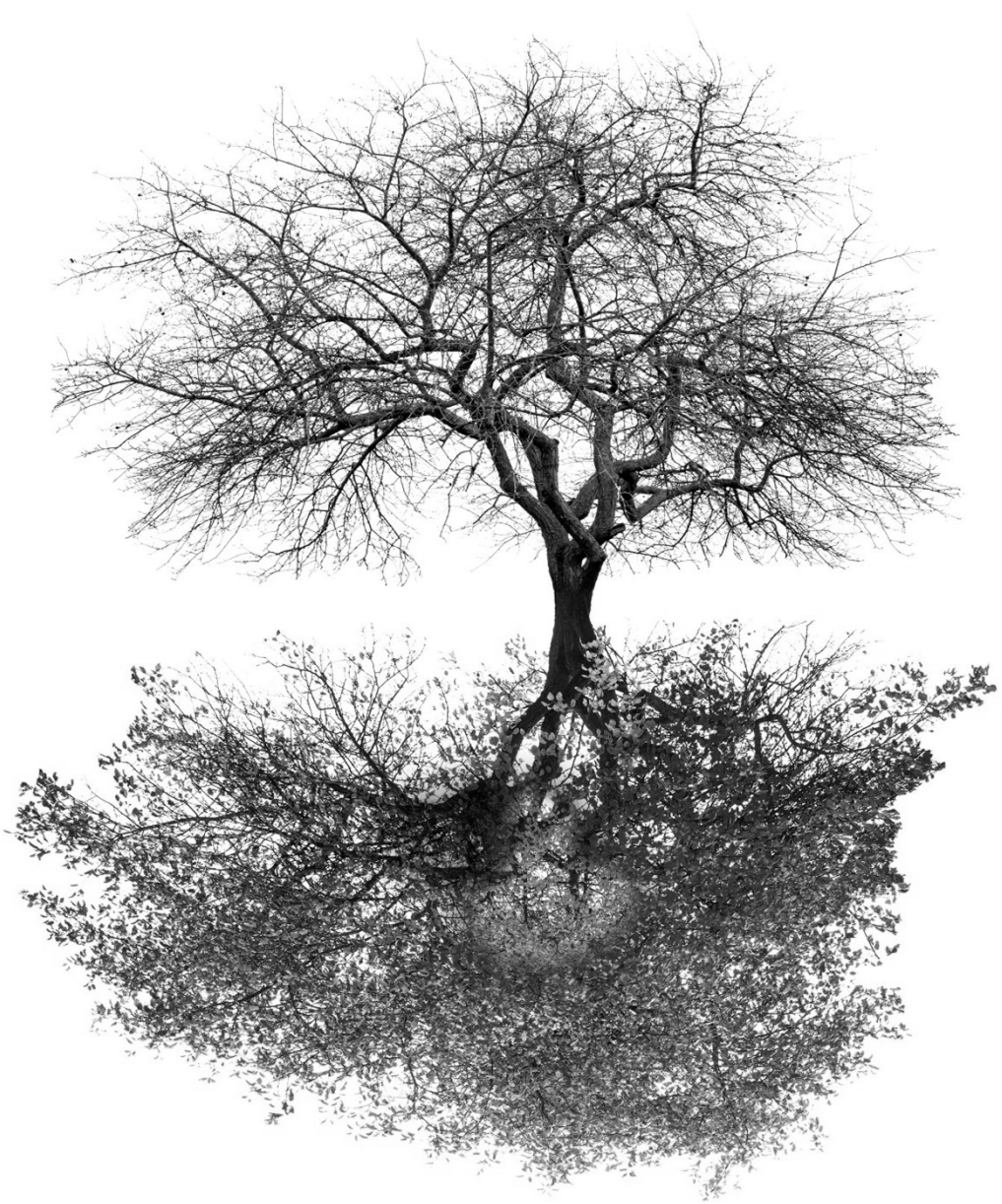
Chapter 7 focused on new subsolid nodules detected in the NELSON trial. Overall, new subsolid nodules were found in <1% of participants with at least one screening after the baseline round. While 6% of participants with a new subsolid nodule had a lung cancer diagnosed in such a nodule, all new subsolid nodule lung cancers detected in the NELSON trial were stage I or adenocarcinoma in situ. This is comparable to baseline nodules and a more aggressive risk-stratification strategy seems not warranted.

Part III - Number of New Nodules and Lung Cancer Probability

Chapter 8 and Chapter 9 assessed whether the number of nodules detected in a lung cancer screening participant affect the lung cancer probability. Around 50% of participants had more than one nodule at baseline and around 20% had more than one new nodule detected. While the new nodule lung cancer probability did not differ significantly between participants with one and more than one new nodule, the new nodule count had a significant negative association with new nodule lung cancer when

assessed together with nodule size. In 97% of participants at baseline and in 100% of participants with new nodules, the lung cancer was found in the largest (new) nodule. However, while risk-stratification should be based on the nodule with the greatest risk of malignancy, all nodules need to be assessed carefully to detect new nodules.

Chapter 10 presents and discusses the main results of this thesis. The implications of the findings are evaluated and summarized in general conclusions and summarized recommendation (Figure). Finally, the impact of the thesis until now is reviewed and future perspectives are presented. So far, results of this thesis were included in a European position statement on lung cancer screening, a Polish consensus statement for the detection of early lung cancer, the British Thoracic Society Guidelines for the investigation and management of pulmonary nodules, the European Society for Medical Oncology Clinical Practice Guidelines for Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer, the new solid nodule management protocol of the Chinese National Lung Cancer Screening Guideline, and the American National Comprehensive Cancer Network guidelines on lung cancer screening.



Chapter 12

Nederlandse samenvatting

Nieuwe nodules bij follow-up low-dose CT longkankerscreening

Deel I – Introductie

In de Verenigde Staten wordt longkankerscreening reeds geadviseerd voor zware (ex-)rokers en in Europa bereidt men zich voor op mogelijke implementatie. Nauwkeurige risicostratificatie is de basis voor elk succesvol screeningsprogramma. Tot voor kort was er weinig kennis omtrent risicostratificatie van longnodules die nieuw gedetecteerd worden na de baseline screeningsronde in een lagedosis computer tomografie (LDCT) longkankerscreeningsprogramma. Doel van dit proefschrift was daarom het in kaart brengen van de risicostratificatie van deze nieuw gedetecteerde longnodules, gebruikmakend van de data verzameld in de grootste Europese longkankerscreeningstudie – de Nederlands-Belgische NELSON studie.

De basis voor dit proefschrift, een overzicht van de huidige kennis over nieuw gedetecteerde longnodules in andere longkankerscreeningsstudies, werd gelegd in **Hoofdstuk 2 en 3.** Er werd geconcludeerd dat de denifitie van een nieuwe nodule, in tegenstelling tot de duidelijk gedefinieerde baselinenodule, varieerde binnen verschillende screeningsstudies. Tevens bleek dat nieuwe nodules vaak niet als zodanig gerapporteerd werden. Het schaarse beschikbare bewijs suggereert dat op jaarbasis 3-10% van de deelnemers aan een longkankerscreeningsprogramma een nieuwe nodule ontwikkelen, en dat zo'n nieuwe nodule in 2-8% van de deelnemers op longkanker blijkt te berusten. Nieuwe nodules ontwikkelen zich in een relatief kort tijdsframe, zeker vergeleken met baselinenodules, die al jaren aanwezig kunnen zijn. Dit impliceert dat nieuwe nodules al bij een kleinere grootte op moment van detectie verdacht zijn voor longkanker.

Deel II – Risicostratificatie van Nieuwe Nodules

In **Hoofdstuk 4** worden het vóórkomen van nieuwe longnodules en de kans op longkanker in zo'n nodule onderzocht in deelnemers van de NELSON studie. Op de jaarlijkse follow-up scan na de baselinescreeningsronde bleek 5% van de NELSON deelnemers een nieuwe nodule te hebben ontwikkeld. In totaal had 11% van de NELSON deelnemers een nieuwe nodule ontwikkeld in de eerste twee follow-up screeningsrondes (tot drie jaar na de baselineronde). In totaal werd in 6% van de deelnemers met een nieuwe nodule longkanker in een nieuwe nodule gediagnosticeerd, 4% van alle nieuwe nodules maligne te zijn. Ter vergelijk: in de

baselineronde kreeg 1% van de NELSON deelnemers de diagnose longkanker, en in de eerste drie rondes 3% van de deelnemers (dit is inclusief deelnemers met longkanker in een nieuwe nodule). Nieuwe nodules hebben dus een hogere maligniteitskans dan baselinenodules, al bij een kleiner volume op moment van eerste detectie. De optimale afkapwaarden voor nodulevolume (95% sensitiviteit) waren <27mm^3 (<1% kans op longkanker, lag risico), 27-206mm^3 (3% kans op longkanker, intermediar risico) en ≥206mm^3 (17% kans op longkanker, hoog risico). Deze afkapwaarden liggen lager dan de corresponderende afkapwaarden voor baselinenodules (<100mm^3, 100-300mm^3, and ≥300mm^3). Samengevat hebben nieuwe nodules een grotere kans om maligne te zijn dan baselinenodules. Voor optimaal longnodulemanagement zijn daarom voor nieuwe nodules lagere afkapwaarden voor nodulegrootte noodzakelijk.

In **Hoofdstuk 5** wordt de optimale methode voor risicostratificatie van nieuwe nodules op de eerste follow-up scan na initiële detectie onderzocht. Meer dan de helft van alle nieuwe nodules bleken spontaan te verdwijnen. De combinatie van nodulevolume en groei (volume-verdubbelingstijd, VDT) zijn goede voorspellers voor de kans op maligniteit. Van de nieuwe solide nodules met volume <200mm^3 op het moment van initiële detectie en ≥200mm^3 tijdens de eerste follow-up scan bleek 38% maligne te zijn. De toevoeging van nodulevolume aan VDT alleen als enige discriminator verbeterde de risicostratificatie significant. De optimale nodulestrategie bleek verwijzing van een person met een nieuwe nodule met VDT <590 dagen en/of een nodulevolume ≥200mm^3. Dit leidde tot 100% sensitiviteit en 84% specificiteit voor de diagnose longkanker.

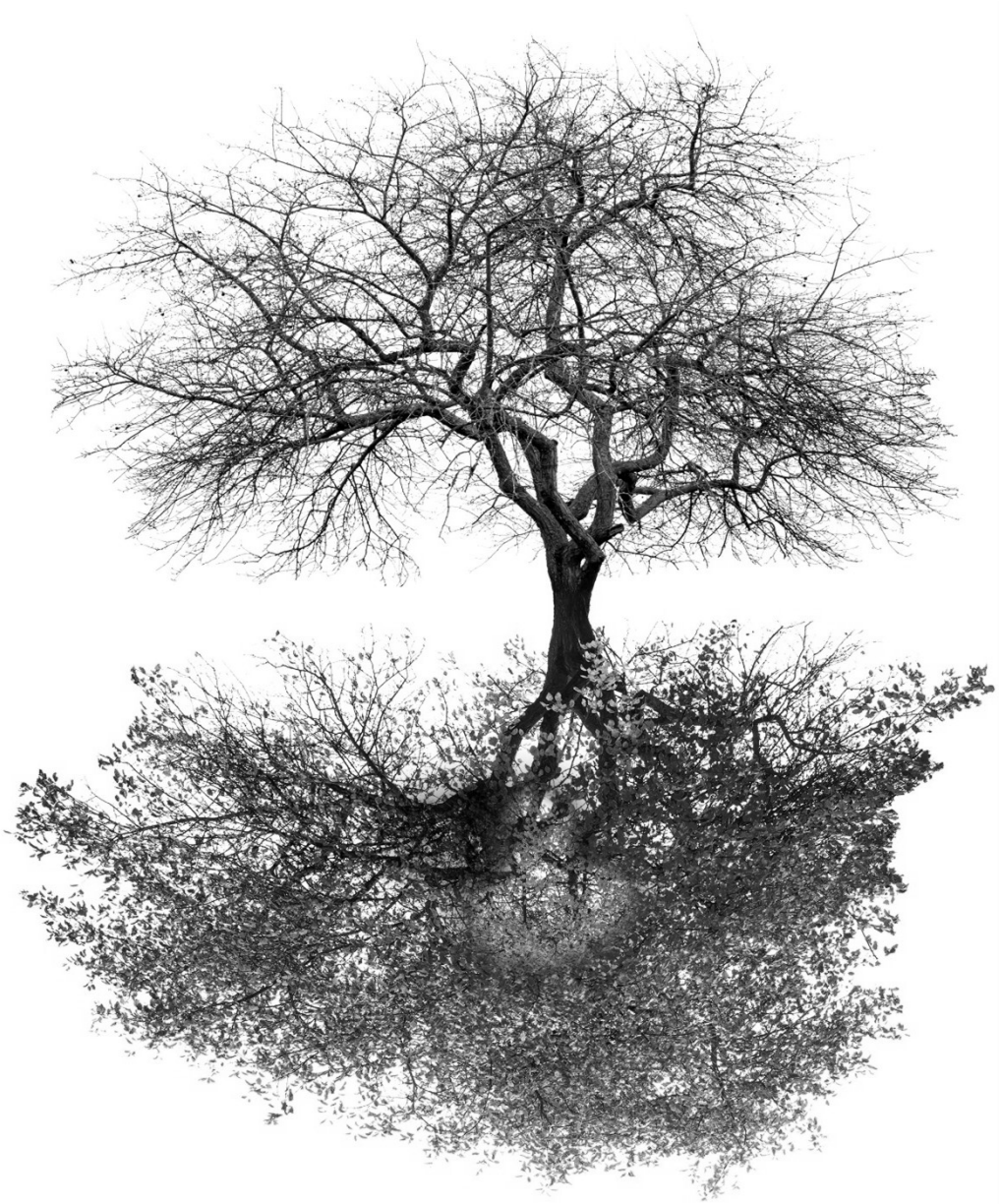
In **Hoofdstuk 6** werden geëvalueerd of er andere nodulekarakteristieken zijn die bijdragen aan de discriminatie van benigne en maligne nieuwe nodules, bovenop de eerder genoemde afkapwaarden voor het nodulevolume (wegens praktische redenen afgerond naar <30mm^3, 30-<200mm^3 en ≥200mm^3). Nodulekarakteristieken die niet beïnvloed worden door nodulegroei, zoals locatie in de rechter bovenkwab en in het centrale deel van de long, bleken een klein positief effect te hebben bovenop nodulevolume op de risicostratificatie. In een risicostratificatie in drie categorieën (laag-, intermediair en hoogrisico) bleek deze toegevoegde waarde van deze extra nodulekarakteristieken echter zeer beperkt te zijn.

Hoofdstuk 7 focust op nieuwe subsolide nodules die gedetecteerd zijn in de NELSON studie. Zo'n nieuwe subsolide nodule werd gedetecteerd in minder dan 1% van alle

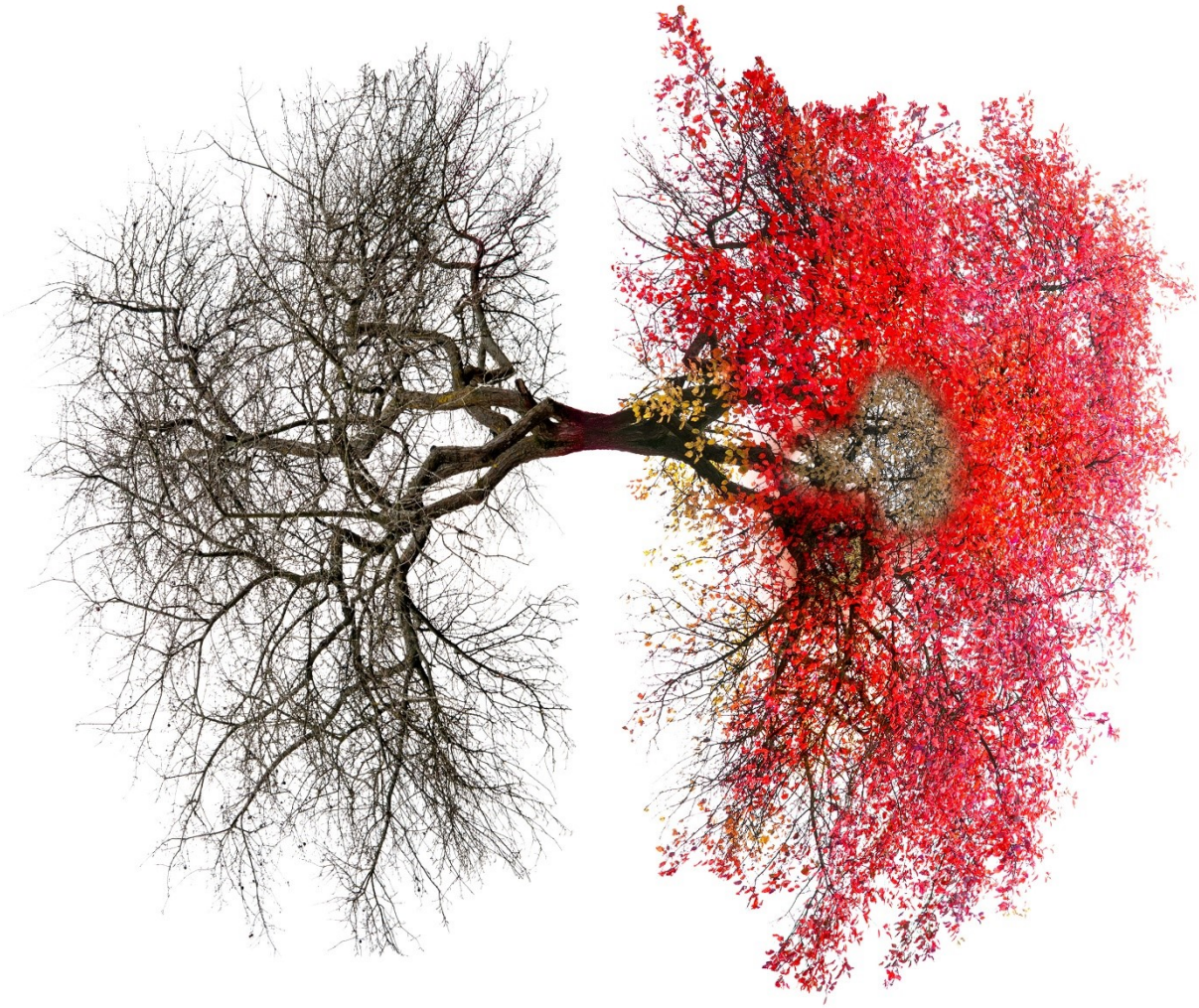
deelnemers met minstens een herhaalscan na baseline. Alhoewel 6% van alle nieuwe subsolide nodules maligne bleken te zijn, waren dit allemaal vroegstadium longkankers op moment van diagnose (stadium I of *in-situ* adenocarcinoom). Deze bevindingen zijn vergelijkbaar met subsolide baselinenodules, en daarom lijkt een meer agressieve vervolgstrategie voor nieuwe subsolide nodules niet nodig.

Deel III – Aantal Nieuwe Nodules en Kans op Longkanker

In **Hoofdstuk 8 en Hoofdstuk 9** wordt onderzocht of het aantal nodules dat gelijktijdig in een deelnemer aan longkankerscreening gedetecteerd wordt van invloed is op de kans op longkanker voor deze persoon. Zo'n 50% van alle deelnemers aan longkankerscreening had tenminste twee gelijktijdig gedetecteerde longnodules, on zo'n 20% van de deelnemers had meer dan een nieuwe nodule. Terwijl het longkankerrisico niet significant verschilde tussen deelnemers met een of meerdere nieuwe nodules, had het aantal nieuwe nodules wel een negatief verband met longkankerrisico wanneer het direct in verband werd gebracht met de grootte van de nodule. Longkankerdiagnose werd in 97% van de deelnemers op baseline en in alle deelnemers met een nieuwe nodule gesteld op basis van de grootste (nieuwe) nodule. Maar hoewel de risicostratificatie daarom gebaseerd moet zijn op de grootste (nieuwe) nodule, is het wel belangrijk om alle, dus ook kleinere, nodules nauwkeurig te rapporteren om zo makkelijker en beter nieuwe longnodules te kunnen identificeren.
In **Hoofdstuk 10** worden de belangrijkste resultaten van dit proefschrift beschreven en in de context van de bestaande literatuur geplaatst. De resultaten van dit proefschrift zijn geïmplementeerd in verschillende (inter)nationale richtlijnen, zoals in de "European position statement on lung cancer screening", in een Pools consensus document aangaande detective van vroegstadium longkanker, in de richtlijn van "the British Thoracic Society", in de richtlijn van het Europees genootschap voor medische oncologie (the European Society for Medical Oncology Clinical Practice Guidelines for Early-Stage and Locally Advanced [non-metastatic] Non-Small-Cell Lung Cancer), in het management protocol voor nieuwe solide longnodules van de "Chinese National Lung Cancer Screening Guideline", en in de richtlijn van het "American National Comprehensive Cancer Network" ten behoeve van longkankerscreening.



Part V
Appendix



Chapter 13

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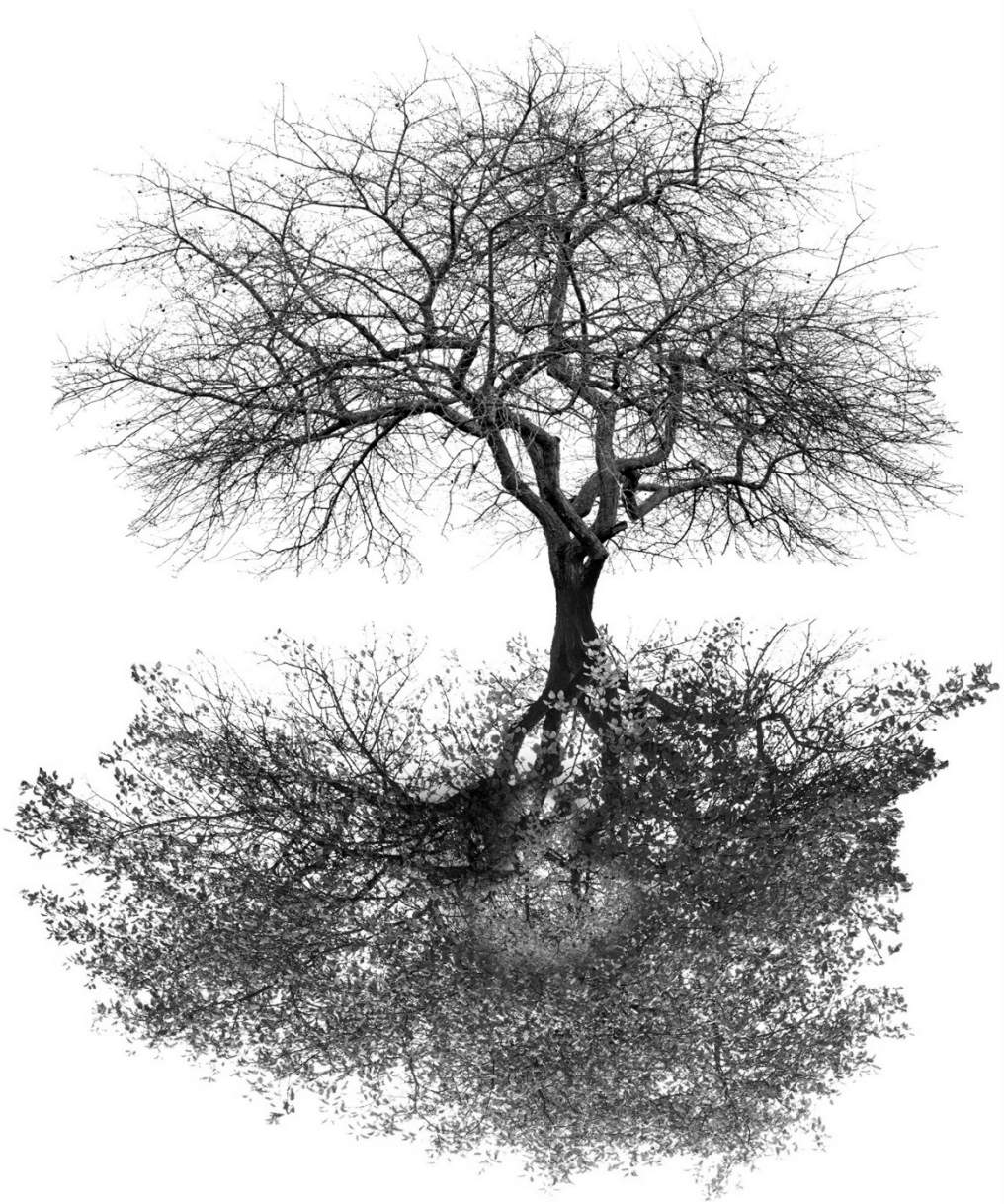

Chapter 14

Curriculum Vitae

Joan Elias Walter was born on December 31h 1989 in Dortmund, Germany. In 2009, he completed secondary school at 'Kaiserin-Augusta-Gymnasium' in Cologne. Subsequently, he performed his civil service at the Institute of Biochemistry, University of Cologne. After walking the camino de Santiago, he started studying Medicine at the University of Groningen in 2011 and graduated Medicine in 2017. Already during his study, he joined the Dutch-Belgian lung cancer screening (NELSON) study team in Groningen and was guided by prof. dr. M. Oudkerk, prof. R. Vliegenthart and dr. M.A. Heuvelmans. His first publication 'Occurrence and lung cancer probability of new solid nodules at incidence screening with low-dose CT' was published in the Lancet Oncology in 2016 (Chapter 4) and forms the backbone of this thesis. Henceforth, he was appointed promovendus at the University Medical Centre Groningen, University of Groningen and focused on new nodules at incidence low-dose CT lung cancer screening in the NELSON trial. Resultant research findings are presented in this thesis.